Study to collect recent information relevant to modernising EU Occupational Safety and Health chemicals legislation with a particular emphasis on reprotoxic chemicals with the view to analyse the health, socio-economic and environmental impacts in connection with possible amendments of Directive 2004/37/EC and Directive 98/24/EC

Final Report

REPORT 1 – BASELINE ASSESSMENT

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Study to collect recent information relevant to modernising EU Occupational Safety and Health chemicals legislation with a particular emphasis on reprotoxic chemicals with the view to analyse the health, socio-economic and environmental impacts in connection with possible amendments of Directive 2004/37/EC and Directive 98/24/EC on the protection of workers from risks related to exposure to carcinogens, mutagens, reprotoxicants and other chemicals at work

March 2019

Final Report
REPORT 1 – BASELINE ASSESSMENT

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Executive Summary

Background to the Study

The EU legislative framework that addresses occupational exposure to Carcinogenic, Mutagenic and Reprotoxic substances includes Directive 98/24/EC (Chemical Agents Directive, CAD) and Directive 2004/37/EC (Carcinogens and Mutagens Directive, CMD). All reprotoxic substances are currently dealt with in the CAD and those that are also Carcinogenic or Mutagenic (C/M) 1A/1B are also within the scope of the CMD. In accordance with a request[1] from the European Parliament and the Council, this study was launched by the European Commission to assess a number of options for amending the CMD, including the possibility of extending its scope to cover all Reprotoxic (R) 1A/1B substances. This included a number of specific tasks which are set out in the Terms of Reference of this study.[2]

Eight EU Member States have extended, in part or in full, their national legislation transposing the CMD to cover reprotoxic substances. This is the case in Austria, Belgium, Czech Republic, Finland, France, Germany, Sweden and the United Kingdom. The situation in these countries ranges from the application of all the requirements in the CMD[3] to reprotoxic substances (Austria and Belgium) to the extension of one or few of the relevant requirements to reprotoxic substances that are not also C/M 1A/1B substances (examples: substitution and record keeping in the United Kingdom, only substitution in Finland). The requirements on reprotoxic substances in the remaining 20 Member States generally mirror those in the CAD. There are also differences between the Member States in terms of how many pieces of legislation they have used to transpose the CAD and CMD (see Section A2 in Main Report 1).

The Burden of Ill-health Under the Baseline

The study adopted two different approaches to estimating the current burden of reproductive ill health from occupational exposure to Reprotoxic 1A/1B substances that are not also C/M 1A/1B[4]:

- under the bottom-up approach[5], 27 to 206 cases are expected to occur each year;
- under the top-down approach[6], 46 to 1,274 cases are estimated to occur each year; and
- when theoretical (unrealistic) worst-case assumptions are adopted for the bottom-up calculations, the figure rises to 1,429 cases per annum.

The economic cost of reproductive ill health is estimated to be between €0.5 and €2.8 million per year under the bottom-up approach and between €39 and €104 million per annum under the top-down analysis.[7] For the theoretical worst case under the bottom-up approach, the figure rises to €381 million per year.

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1 Directive (EU) 2017/2398, see https://eur-lex.europa.eu/eli/dir/2017/2398/oj

2 See https://etendering.ted.europa.eu/document/document-file-download.html?docFileId=36431

3 For example, substitution whenever exposure is likely, closed systems, exposure minimisation, keeping certain records for 40 years.

4 Reprotoxic (R) 1A/1B substances that are not also Carcinogenic or Mutagenic (C/M) 1A/1B are substances that are currently within the scope of the CAD only. R1A/1B substances that are not also C/M 1A/1B are also within the scope of the CMD due to their carcinogenic or mutagenic classification.

5 The bottom-up approach relies on extrapolations from a set of 30 shortlisted Reprotoxic 1A/1B substances.

6 The top-down approach draws on the use of population level incidence and prevalence data for health effects linked to exposures to reprotoxic substances.

7 This includes the direct, indirect, and intangible costs for workers & families, employers and the public sector.

The bottom-up approach suggests that lead and lead compounds account for a large proportion of the total annual number of cases of reproductive ill health estimated in this study. The implication is that, although this report considers the potential benefits from the inclusion of Reprotoxic 1A/1B substances into the scope of the CMD, a large part of the burden of reproductive ill health could be eliminated by means of lowering the Biological Limit Value (BLV) and the Binding Occupational Exposure Limit Value (BOELV) for lead under the CAD and ensuring compliance with the revised limit values.

Summary of the Policy Options

The Policy Options assessed in this report are:

Option 1- (baseline without additional guidance): No changes to EU Occupational Safety and Health (OSH) legislation and no additional OSH guidance;

Option 1 (baseline including additional guidance): No changes to EU OSH legislation, additional OSH guidance at EU level;

Option 2: Extending the CMD to all Reprotoxic 1A/1B substances;

Option 3: Extending the CMD to all Reprotoxic 1A/1B substances but providing derogations from key requirements. These derogations would be revoked for individual substances for which the absence of a threshold for reproductive effects is established by an EU scientific committee;

Option 3+: Based on the Cefic[8]/ECEG[9]/ETUC[10]/IndustriAll[11] declaration[12] - extending the CMD to all Reprotoxic 1A/1B substances, always applying requirements on substitution and closed systems, possibility of a derogation from the exposure minimisation requirement in the event of compliance with a health-based BOELV;

Option 4: Merging the CAD and CMD into a single piece of legislation and applying CMD-equivalent requirements to all Reprotoxic 1A/1B substances; and

Option 5: Merging the CAD and CMD into a single piece of legislation, applying CMD-equivalent requirements to all Reprotoxic 1A/1B substances, updating/modernising OSH terms and requirements, and introducing several add-on elements (including breaking the link between mandatory use of health surveillance and BLVs and applying a non-threshold approach to respiratory and skin sensitisers).

Further details on the Policy Options are provided in Table 1.

[8] The European Chemical Industry Council
[9] The European Chemical Employers Group
[10] The European Trade Union Confederation
[11] IndustriAll European Trade Union
[12] See https://www.etuc.org/sites/default/files/press-release/file/2018-10/Joint%20Declaration%20Reprotoxics%20signed.pdf

Table 1: Policy Options	
Option	**Details**
O1-: Baseline, no OSH guidance	No changes to EU OSH legislation but exposure may change due to other legislation and market developments. No additional guidance provided
O1: Baseline (no changes to EU OSH legislation, guidance)	No changes to EU OSH legislation but exposure may change due to other legislation and market developments. Provision of additional guidance on best available techniques and interpretation of the CMD/CAD

O2: R 1A/1B in CMD (no derogations)	Inclusion of R 1A/1B chemicals into the scope of the CMD with full application of the requirements in the CMD, including:
	- Substitution: stricter requirement than in the CAD:
	  ○ mandatory whenever workers 'are or are likely to be exposed'
	  ○ 'risk > slight risk' not a prerequisite
	- Closed system: second RMM in the hierarchy under the CMD vs. no explicit reference to closed systems in the CAD (except for intermediates);
	- Reduction of exposure to as low as technically feasible (minimisation requirement);
	- IOELVs for R1A/1B substances would become BOELVs: IOELVs under the CAD for R1A/1B substances would become BOELVs under the CMD; and
	- Record keeping: Record keeping for at least 40 years would be required for R 1A/1B substances.

O3: R 1A/1B in CMD with derogations	Inclusion of R 1A/1B into the scope of the CMD but with derogations from the substitution, closed system, minimisation and record keeping requirements, unless an EU scientific committee confirms the substance has no threshold for reprotoxic effects. CAD IOELVs for R 1A/1B substances become BOELVs under the CMD.
O3+: Cefic/ECEG/ETUC/ IndustriAll Declaration: R 1A/1B in CMD with derogations	Inclusion of R 1A/1B into the scope of the CMD with the following requirements: - A Binding OELV (risk or health based) would be established for Rs; - CMD requirements on prevention (substitution, closed system) would always apply to reprotoxic substances; - If prevention were not possible, then exposure must be reduced to a) a 'safe level' (see below) or b) as low as possible (minimisation requirement); - Safe level: a) the substance has a threshold, b) there is a health-based Binding OELV (including CAD IEOLVs->CMD BOELVs), c) it is proven by exposure measurements that the BOELV is complied with; - Differentiated approach (non-threshold vs safe level) should also be applied to C/M.
O4: Merge CAD & CMD into a single directive but no modernisation	Merging the CMD and CAD into a single directive, applying CMD-equivalent requirements to R 1A/1B substances but no further changes: - This would effectively be CAD and CMD in parallel but in one document; - Old terminology: language would not be updated or modernised; - CMD-equivalent requirements would apply to CMR 1A/1B substances and CAD requirements would apply to other hazards.
O5: Merge CAD & CMD and modernise	Merging the CMD and CAD, applying CMD-equivalent requirements to R 1A/1B substances and updating/modernising OSH terms and requirements: - CMD-equivalent requirements apply to CMR 1A/1B substances and CAD-equivalent requirements apply to other types of hazardous substances; - Common terminology for substances subject to CMD-equivalent and CAD-equivalent requirements; - Terminology brought into line with REACH; and - Add on elements: a) skin and respiratory sensitisers would also be subject to CMD-equivalent requirements and b) use of BLVs as part of health surveillance would not be mandatory.

Costs of the Policy Options

No additional costs would arise under Option 1-. The guidance developed under Option 1 is expected to result in some additional costs for public authorities and companies. With regard to the inclusion of Reprotoxic 1A/1B substances into the CMD, the more stringent requirements of the CMD have the potential to increase compliance costs for companies in the Member States where these requirements are not currently applied to Reprotoxic 1A/1B substances that are not also C/M 1A/1B. The cost of some of these measures, expressed as an annualised cost, has been estimated at between €400 million and €900 million, as indicated in Table 2.[13] These figures include the costs of considering and documenting the feasibility of substitution and closed systems, as well as implementing closed systems and further measures to minimise exposure. These costs are likely to arise under Options 2, 3+, 4 and 5, all of which involve the extension of the CMD to cover Reprotoxic 1A/1B substances.

Table 2: Costs under the different Policy Options
Legend: ++++: very high costs, +++: high costs, ++: medium costs, +: limited costs, 0: no costs

Aspect ↓	Policy Option →		O1-	O1	O2	O3	O3+	O4	O5
Costs for companies (annualised cost)									
Additional OSH guidance			0	++	++	++	++	++	++
Extension of CMD to R 1A/1B	Substitution	Consideration	0	0	++ (€10-20m)	+	++ (€10-20m)	++ (€10-20m)	++ (€10-20m)
		Implementation	0	0	Potentially ++++	++	Potentially ++++	Potentially ++++	Potentially ++++
	Closed systems	Consideration	0	0	+++ (€180-260m)	++	+++ (€180-260m)	+++ (€180-260m)	+++ (€180-260m)
		Implementation	0	0	++ (€60-240m)	++	+++ (€60-240m)	+++ (€60-240m)	+++ (€60-240m)
	Exposure minimisation		0	0	+++ (€80-250m)	++	++ (less than O2, 4, 5)	+++ (€80-250m)	+++ (€80-250m)
	11 CAD Indicative OELVs -> CMD Binding OELVs		0	0	+	+	+	+	+
	Record keeping		0	0	++ (€80-140m)	+	Unknown	++ (€80-140m)	++ (€80-140m)
Additional BOELVs			+	+	+	+	++++	+	+
Merging of the two directives			0	0	0	0	0	+	+
Substance-by-substance threshold vs non-threshold approach			0	0	+++	0	++	+++	+++
Modernisation of terms			+	+	+	+	+	+	Unknown
Add-on elements	Health surveillance/ Biological Limit Values		0	0	0	0	0	0	Unknown
	Non-threshold approach for sensitisers		0	0	0	0	0	0	Potentially +++
Public authorities (total cost in € million)									
EU – development of OSH guidance			0	€10m	€10m	€10m	€10m	€10m	€10m
Member States – transposition cost			0	0	€3m	€3m	€3m	€3m	€3m

In the absence of scientific evaluations for all the relevant substances, it is not possible to determine which specific substances would be included into the scope of the CMD requirements under Option 3. The costs of Option 3 are likely to be lower than those of Options 2, 3+, 4 and 5 but greater than under Options 1- and 1. In addition, the costs of Option 3 would be staggered as specific non-threshold substances are included into the scope of the relevant requirements over time. Option 3+ can be expected to be the most costly method of extending the CMD to Reprotoxic 1A/1B substances, since it is likely to accelerate the process of adoption of Binding Occupational Exposure Limit Values (BOELVs) for Reprotoxic 1A/1B substances that are not also C/M 1A/1B. Although it is expected that

[13] Due to the large number of uncertainties involved in the estimation of the costs, the quantified ranges in Table 2 are illustrative of the magnitude of the potential impacts rather than definite estimates.

additional BOELVs would also be adopted under the other options, earlier adoption of BOELVs under Option 3+ would result in greater overall compliance costs for companies; these would include the need to prove compliance through exposure measurements for companies in which exposure is already below the thresholds for effects.

Benefits of the Policy Options

No reduction in ill-health is expected under Option 1-. Increased uptake of 'best practices' under Option 1 is expected to reduce reproductive ill health but not as much as Options 2, 3, 3+, 4 and 5.

The more stringent requirements in the CMD (differences between the substitution requirements, explicit reference to closed systems and the requirement to minimise exposure, etc.) have a potential to reduce reproductive ill health in the Member States where these requirements are not yet applied to Reprotoxic 1A/1B substances. There is, however, a large degree of uncertainty about the extent of this reduction, which has been estimated to be between 1 and 380 cases of reproductive ill health per year. These have a total monetary value between €20,000 and €31 million annually due to direct, indirect, and intangible costs for workers, their families, employers and the public sector.[14] A comparison of the policy options for each benefit impact category is provided in Table 3. These benefits are likely to occur under Options 2, 3+, 4 and 5, all of which involve the extension of the CMD to all Reprotoxic 1A/1B substances. Option 3+ is expected to be the most effective option in terms of reducing reproductive ill health since it is likely to result in an earlier adoption of BOELVs for Reprotoxic 1A/1B substances that are not also C/M 1A/1B. Reductions in ill health under Option 3 would commence later as individual substances are identified one by one as having no threshold for reprotoxic effects and thereby being subject to the relevant requirements of the CMD.

[14] Due to the large number of uncertainties involved in their estimation, the benefits estimated in Table 3 are illustrative of the magnitude of the potential impacts rather than definite estimates.

Table 3: Benefits of the different Policy Options

Key: ++++ substantial benefits, +++ significant benefits, ++ some benefits, + limited benefits, 0 no change.

Aspect ↓	Policy Option →	Relevant stakeholders	O1-	O1	O2	O3	O3+	O4	O5
Reduced ill health due to OSH guidance		Workers & families	0	++	++	++	++	++	++
Health benefits from extension of the CMD to R1A/1B substances	Substitution and closed systems		0	0	++ 1-191 avoided repro cases p.a. €0.02-16m p.a.	++ Not possible to quantify but less than under O2, O3+, O4, and 05	++ 1-191 avoided repro cases p.a. €0.02-16m p.a.	++ 1-191 avoided repro cases p.a. €0.02-16m p.a.	++ 1-191 avoided repro cases p.a. €0.02-16m p.a.
	Exposure minimisation		0	0	++ 4-191 avoided repro cases p.a. €0.08-16m p.a.		++ 4-191 avoided repro cases p.a. €0.08-16m p.a.	++ 4-191 avoided repro cases p.a. €0.08-16m p.a.	++ 4-191 avoided repro cases p.a. €0.08-16m p.a.
	40 years of record keeping	Authorities	0	0	++	+	0	++	++
	11 CAD IOELVs -> CMD BOELVs	Workers & families	0	0	0	0	0	0	0
Additional OELVs for R1A/1B substances		Companies, authorities	++	++	++	++	+++	++	++
Add-on elements (Biological Limit Values and sensitisers)		Workers and their families	0	0	0	0	0	0	+++
Reduced absenteeism		Companies	0			Included in health-related benefits (see above)			
Reduced healthcare and social sec. expenditure		Authorities	0						
Administrative simplification		Companies	0	+	++	+++	+++	+++	++++
Administrative simplification – legal coherence		Authorities	0	+	++	+++	+++	+++	++++
Administrative simplification – ease of enforcement		Authorities	0	+	++	+	++	++	+++
Level playing field		Companies	0	+	+++	++	++++	+++	+++
Fundamental rights		Workers & families	0	+	+++	++	+++	+++	+++
Modernisation of terms		Authorities, companies, workers	0	0	0	0	0	0	+++
Individual substance approach (Threshold vs Non-threshold)		Companies	0	0	Significant negative impact	++	++ (but +++ if extended to C/M)	Significant negative impact	Significant negative impact
Overall health benefits for R1A/1B substances		***Workers & families, companies, authorities***	***0***	***+***	***+++ 1-382 avoided repro cases p.a.[1] €0.02-31m p.a.***	***++ Not quantified but less than under O2, O3+, O4, O5***	***+++ 1-382 avoided repro cases p.a.[1] €0.02-31m p.a.***	***+++ 1-382 avoided repro cases p.a.[1] €0.02-31m p.a.***	***+++ 1-382 avoided repro cases p.a.[1] €0.02-31m p.a.***

Notes: p.a.: per annum; IOELV: Indicative Occupational Exposure Limit Value; BOELV: Binding Occupational Exposure Limit Value

1: The low end of the sum of avoided cases does not take into account exposure minimisation since these benefits are highly uncertain

Comparison of the Policy Options

Due to the large number of uncertainties involved in the estimation of the costs and benefits, the quantified ranges presented in this report should be seen as illustrative of the magnitude of the potential impacts rather than definite estimates. In addition, some relevant (and potentially significant) costs and benefits could not be monetised, including benefits from reducing other types of health effects. Furthermore, the impacts of the extension of the CMD to cover Reprotoxic 1A/1B substances to a large extent depend on transposition and enforcement decisions taken at the Member State level, and these cannot be predicted with any degree of certainty.

No change in the current costs and benefits is expected under Option 1-. Although the precise magnitude of the costs and benefits under Option 1 is uncertain (these depend on voluntary uptake of best practice measures), it can be expected that any benefits would be accrued in an efficient manner, i.e. unnecessary compliance costs for companies would be avoided.

Under Options 2, 3+, 4 and 5, the quantified costs outweigh the quantified benefits – in some cases, this difference can be quite significant. This conclusion does not change when qualitative scores and uncertainties for which there is some indication of their order of magnitude are taken into account. Option 3+ is expected to be the most effective option in terms of reducing reproductive ill health since it should lead to an earlier adoption of BOELVs for Reprotoxic 1A/1B substances that are not also C/M 1A/1B. It is, however, also likely to be the costlier option as a large number of companies would have to demonstrate compliance with the BOELVs. The costs under Option 3 are likely to be lower but, in the absence of scientific evaluations for all the relevant substances, it is not possible to determine which specific substances would be subject to CMD requirements. In addition, under Option 3, the costs and benefits would be staggered over time.

Under Options 2, 3, 3+, 4 and 5, the method of extending the CMD to cover Reprotoxic 1A/1B substances means that some companies would incur costs but would see no reductions in reproductive ill health since their workers are already exposed at levels below the thresholds for reproductive effects. This is a consequence of the extension of a non-threshold approach to threshold substances. The exemption from the exposure minimisation requirement under Option 3+ for companies that can demonstrate a 'safe level' of exposure would mitigate these costs but substantial costs would still be incurred in demonstrating compliance with BOELVs and due to the substitution and closed system requirements under the CMD. Option 3 avoids these consequences and, thus, is the one, apart from the baseline options, least likely to result in unnecessary costs. However, reductions in ill health would be delayed under Option 3 as a determination by an EU scientific body would be necessary for CMD requirements to apply to non-threshold Reprotoxic 1A/1B substances. Furthermore, in the absence of scientific evaluations for all the relevant substances, it is not possible to determine which specific substances would be included into the scope of the CMD requirements.

Illustrative case studies

The study includes illustrative case studies for the following substances: lead and lead compounds, borates and retinol. The case studies show that, while a very large workforce is exposed to borates and retinol, they are typically exposed at very low levels (although some data limitations have to be recognised). As a result, no cases of reproductive ill health have been estimated for these substances under any of the realistic scenarios. However, due to the large number of companies, even limited costs on a per company basis due to the need to document feasibility of substitution/closed systems have the potential to result in significant overall costs.

The lead case study, on the other hand, is an example of a comparately smaller occupationally exposed population (although it should be recognised that data are not available for some sectors) which accounts for a large proportion of the annual number of cases of reproductive ill health predicted as arising from exposures to the 30 substances under the bottom-up approach.

Glossary of key acronyms

Acronym	Explanation
BLV	Biological limit value
BOELV	Binding Occupational Exposure Limit Value
CAD	Directive 98/24/EC - Chemical Agents Directive,
Cefic	The European Chemical Industry Council
C/M	Carcinogenic and Mutagenic
C/M 1A/1B	Carcinogenic 1A/1B and Mutagenic 1A/1B substances
CMD	Directive 2004/37/EC - Carcinogens and Mutagens Directive
CMR 1A/1B	Carcinogenic 1A/1B, Mutagenic 1A/1B and Reprotoxic 1A/1B substances
ECEG	The European Chemical Employers Group
ETUC	The European Trade Union Confederation
IndustriAll	IndustriAll European Trade Union
IOELV	Indicative Occupational Exposure Limit Value
OELV	Occupational Exposure Limit Value
OSH	Occupational Safety and Health
R 1A/1B	Reprotoxic 1A/1B substances
REACH	The REACH Regulation (EC) No 1907/2006

Summary Report

Background to the Study

The EU legislative framework that addresses occupational exposure to Carcinogenic, Mutagenic and Reprotoxic substances includes Directive 98/24/EC (Chemical Agents Directive, CAD) and Directive 2004/37/EC (Carcinogens and Mutagens Directive, CMD).

All reprotoxic substances are currently dealth with in the CAD and those that are also Carcinogenic or Mutagenic (C/M) 1A/1B are also within the scope of the CMD. In accordance with a request[15] from the European Parliament and the Council, this study was launched by the European Commission to assess a number of options for amending the CMD, including the possibility of extending its scope to cover all Reprotoxic (R) 1A/1B substances. This included a number of specific tasks which are set out in the Terms of Reference of this study.[16]

The main objective of this study is to generate the evidence to enable the European Commission to initiate policy discussions regarding the possible future amendment of the CMD in order to include in its scope Reprotoxic 1A and 1B substances and/or, based on a possible merger of the CMD and CAD, additional requirements that would be necessary to address risks from Reprotoxic 1A/1B substances. In addition, several add-on tasks that could be considered as part of a more general revision of the Occupational Safety & Health (OSH) system have been included into the scope of this study, as set out in the Terms of Reference[17].

EU and National Regulatory Systems

The key features of the regulatory systems seeking to protect workers from risks arising from occupational exposure to Reprotoxic 1A/1B substances at the EU level, in EU Member States, non-EU European Economic Area (EEA) countries (Norway, Iceland and Liechtenstein) and selected third countries that are major EU trading partners are summarised in this report. Based on the comparison of the key features between the CAD and the CMD, the main differences between the two Directives that are relevant to the Impact Assessment part of this study rest upon the following elements:

- The starting points triggering the application of the Directives;
- The level of exposure that signifies risk;
- The circumstances in which substitution should be considered;
- The criteria for deciding on substitutability;
- The Risk Management Measures applicable where substitution is not required; and
- The types of Occupation Exposure Limit values established under the Directives.

When looking at national transposition of the CAD and the CMD, the Member States have broadly selected one of the following approaches to transposition:

- National measures that transpose the two Directives in two separate legal instruments (10 Member States);

[15] Directive (EU) 2017/2398, see https://eur-lex.europa.eu/eli/dir/2017/2398/oj
[16] See https://etendering.ted.europa.eu/document/document-file-download.html?docFileId=36431
[17] See https://etendering.ted.europa.eu/document/document-file-download.html?docFileId=36431

- National measures that transpose the two Directives in one legal instrument (5 Member States); and
- Implementation in a series of national measures (13 Member States).

Eight EU Member States have taken advantage of the fact that the CAD and CMD are 'minimum harmonization' directives and have extended, in part or in full, their national legislation transposing the CMD to cover reprotoxic substances. This is the case in Austria, Belgium, Czech Republic, Finland, France, Germany, Sweden and the United Kingdom. The situation in these countries ranges from the application of all the requirements in the CMD[18] to reprotoxic substances (Belgium) to the extenstion of one or a few of the relevant requirements to reprotoxic substances that are not also C/M 1A/1B substances (examples: substitution and record keeping in the United Kingdom, only substitution in Finland). The requirements on R substances in the remaining 20 Member States generally mirror those in the CAD. There are also differences between the Member States in terms of how many pieces of legislation they have used to transpose the CAD and CMD.

When analysing national transpositions of the CAD and the CMD, this report has looked at the technical manner in which the directives were implemented by the EU Member States, referred to as the 'typology of national measures in the EU', and how such EU Member States regulate reprotoxic substances. To that effect, certain categories were established. However, it must be noted that for certain countries, a clear answer may not always be achievable and, depending on the data and criteria used, alternative classifications of Member States could be possible. In that regard, it is notably not always possible to a draw clear conclusion as to whether some Member States have extended the CMD requirements to Reprotoxic 1A/B substances, and/or the extent thereof.

Threshold versus Non-threshold Paradigm

One of the issues considered in this report is whether the current paradigm of threshold (T)[19] acting substances addressed by CAD and non-threshold (NT) acting substances addressed by CMD is still relevant, efficient and effective at controlling risks to workers' health.[20] This includes the question of whether, as a default approach (i.e. unless proven otherwise for specific substances), reproductive effects should be presumed to have a threshold. It is, however, recognised that the T vs NT distinction is only one of a number of reasons for the differences between the CAD and CMD approaches, alongside other aspects such as the severe health consequences of C/M substances.

This report concludes that the differentiation between threshold and non-threshold effects is still relevant, effective and efficient for the purposes of EU OSH legislation. However, recent developments in scientific knowledge show that some carcinogens are now assumed to act through a threshold Mode of Action (MoA), which suggests that the determination of the most appropriate approach should be carried out on a substance-by-substance rather than hazard classification basis.

Drawing on a review of scientific literature, this report argues that the T approach continues to be an adequate default approach for reproductive effects, although there may be a small number of

[18] For example, substitution whenever exposure is likely, closed systems, exposure minimisation, keeping certain records for 40 years.

[19] The term 'threshold' means a dose or concentration, below which adverse effects of a substance are not expected to occur.

[20] It should be noted that this is only one of several distinctions between the CAD and CMD, one of the other ones being the severe health consequences that carcinogens can have.

substances for which an NT approach may be more appropriate (this underscores the usefulness of determining which of the two approaches is more suitable on a substance by substance basis). This conclusion takes into account the fact that a small number of reprotoxic substances can act through an endocrine disrupting MoA and, as recognised in the recent Communication from the Commission COM(2018) 734[21], there is an ongoing debate about what should be the most suitable paradigm for risk characterisation of Endocrine Disrupting Chemicals (EDCs). In addition, although the T approach is deemed to be an adequate default approach, the value of the threshold may in some instances be difficult (or impossible) to determine or may be close to (or below) background exposure levels, suggesting that, in these cases, the NT approach to controlling risk may be more appropriate.

As an add-on to the core analysis, the need for the extension of the NT approach to other types of chemical hazards is briefly considered on the example of sensitisers. The majority opinion of the experts and authorities appears to be that, for skin sensitisers, thresholds for induction for sensitisation exist and it is likely that health-based reference values based on the threshold assumption would be determined (despite some methodological difficulties). For respiratory sensitisers, thresholds for adverse effects (induction of sensitisation) exist but are difficult to determine with currently available models and methods, suggesting that the NT approach would be the more practical approach in terms of controlling risks from occupational exposure.

The conclusions in this study reflect what appears to be the prevailing scientific opinion. However, it is recognised that there is a diversity of scientific opinions on some of the relevant issues and there may be a minority scientific opinion that is not in agreement with the findings in this study. In particular, there is a range of opinions regarding whether thresholds exist for adverse effects that occur via the endocrine disruption MoA, as recognised in COM(2018) 734.

Estimating the Burden of Ill-health

The study adopted two different approaches to estimating the current burden of reproductive ill-health from occupational exposure to Reprotoxic 1A/1B substances that are not also C/M 1A/B[22]:

1. The first method involves adopting a **top-down** approach, drawing on the use of population level incidence and prevalence data for health effects linked to exposures to reprotoxic substances. These prevalence data are adjusted to derive the potential maximal burden of effects that can be attributed to occupation exposure.

2. The second method is based on a **bottom-up** approach. It develops estimates for a set of 30 shortlisted Reprotoxic 1A/1B substances. For these selected substances, dose-response relationships for different effects identified from the toxicological literature have been developed. These have then been combined with data on uses, exposures (including from monitoring data), and numbers of workers likely to be exposed.

Note that for both approaches, we have also quantified the health burden in terms of the associated disability adjusted life years (DALYs) and/or using willingness to pay and cost of illness estimates.

[21] See http://ec.europa.eu/transparency/regdoc/rep/1/2018/EN/COM-2018-734-F1-EN-MAIN-PART-1.PDF

[22] Reprotoxic (R) 1A/1B substances that are not also Carcinogenic or Mutagenic (C/M) 1A/1B are substances that are currently within the scope of the CAD only. R1A/1B substances that are not also C/M 1A/1B are also within the scope of the CMD due to their carcinogenic or mutagenic classification.

Top down Estimates

The potential burden of health effects associated with occupational exposures to Reprotoxic 1A/1B substances, as calculated using the top-down approach, can be summarised as follows:

- A wide range of potential effects have been identified as being relevant to Reprotoxic 1A/1B substances, with these including impacts on male and female infertility, neo- and post-natal effects, as well as a range of congenital anomalies in newborn children. Exposures to Reprotoxic 1A/1B substances are not the only risk factors for such effects, however, with other maternal and environmental factors including smoking, obesity and diabetes. In addition, it must be remembered that exposures to reprotoxic substances may not only occur in the workplace.

- Based on a 2010 self-reporting survey (the so-called Sumer survey) carried out on the French labour force:

  - 1.1% of workers self-reported that they were exposed to a selected group of Reprotoxic 1A/1B substances (lead, glycol ethers, phthalates NMP, DMF and DMAC) that are also not classified as carcinogens and mutagens;
  - Although this may represent the population that may be exposed, this does not mean that these workers are exposed at levels which would give rise to effects. Indeed, the data indicate that only a very small percentage of this 1.1% of workers is actually exposed at significant intensities (i.e. above the threshold for effects) and durations to the group of substances; thus, one would expect the potential for impacts to be very low;
  - Extrapolation up from the French data to the EU level and multiplied by two account for other Reprotoxic 1A/1B substances that are also not classified as carcinogens or mutagens leads to estimates that between 22,000 and 61,000 male workers (0.015 – 0.043%) and 3,000 and 8,000 female workers (0.003 - 0.007%)(based on geometric means and with and without welding) are anticipated as being exposed long enough and to levels that may be high enough to give rise to reprotoxic effects (i.e. at levels above the threshold for effects);

- Combining figures on the predicted EU population that may be exposed to Reprotoxic 1A/1B substances at levels that may give rise to effects, as well as adjusting for the percentage of women getting pregnant in any one year, results in the following estimated cases:

  - Fertility effects: between 39 and 1,055 cases of infertility or babies not being carried to term;
  - Developmental effects: between 7 to 219 cases of developmental effects.

There are some important limitations to this top-down assessment. It is based on data for only one country and may therefore not be representative of worker exposures across the EU as a whole. It is also based on only a subset of Reprotoxic 1A and 1B substances not also classified as carcinogens and mutagens although, as discussed in Section B2 below, these include substances that are expected to account for the majority of workplace risks from exposure to Reprotoxic 1A/1B substances. In addition, within the reported data, there are significant numbers of entries which are "not declared" or missing. The reasons for these could range from ignorance to a reluctance to report.

On the other hand, the top-down approach relies on incidence or prevalence rates in the general population and estimates the theoretical maximum number of cases by deducting known non-

occupational causes and applying the resulting incidence rates to the occupationally exposed population. This approach relies on sufficient data being available for non-occupational causes and, as a result, entails a potential for overestimation. Adjustments have also been made to ensure that the population taken into account is of reproductive age; similarly, for developmental effects, it is important to only consider the proportion of births to women within the working population.

All of these adjustments lead to uncertainties. For example, it has not been possible to adjust the data for all known non-occupational causes of infertility and developmental effects, as such an approach would rely on the availability of specific attributable fraction data for those causes; this leads to the potential for overestimation.

Bottom up Estimates

The estimates developed for this approach are based on detailed evaluation of 30 substances. Dose-response relationships and thresholds for different reprotoxic effects were developed for each substance and these were combined with data on levels of control in the workplace and the number of workers likely to be exposed.

The potential burden of health effects associated with occupational exposures to Reprotoxic 1A/1B substances that are not also Carcinogens or Mutagens, as calculated using the bottom-up approach, can be summarised as follows:

- At the start of the study (March 2018), a total of 194 substances was identified as Reprotoxic 1A/1B substances registered under REACH. After removing those also classified as Carcinogenic 1A/1B or Mutagenic 1A/1B (43 substances), those already restricted for reasons relevant to occupational exposures or going through Authorisation (12 non-CMR substances) and some self-classified substances, a long list of 52 fully registered/intermediate substances was developed. Substances in this list were prioritised based on consideration of risk (based on tonnages and Derived No Effect Levels), three aprotic solvents were added and a final list of 30 substances was developed;

- These substances may be used in 36 different industry sectors, with individual substances likely to be used in multiple sectors and many of the sectors being likely to use more than one of the substances;

- Data provided by industry (individual companies and associations), collected from CSRs and from the literature indicate that exposure levels are expected to be at levels below the thresholds for effects in most workplaces;

- After applying dose-response relationships and thresholds developed for each of the substances and different health effects (from information provided in the CSRs or SCOEL and RAC opinions), between 24 and 180 cases of reproductive ill health per annum were predicted as arising from exposures to the 30 substances and depending on exposure scenario. When extrapolated to other Reprotoxic 1A/1B substances that are not also Carcinogenic or Mutagenic 1A/1B substances, this figure rises to between 27 and 206 cases of reproductive ill health per annum.

- Finally, it has only been possible to estimate the potential cases of reprotoxic effects that are currently associated with workplace exposures. Exposures to reprotoxic chemicals at levels below the threshold for reprotoxic effects may lead to other health effects not considered

here. Where this is the case, there will be an additional burden of ill health not captured by this study.

The bottom up approach reflects cases for which there is sufficient data and, consequently, it has the potential for underestimation. Dose-response functions can only be developed for the effects for which there are sufficient data in published scientific studies, measured exposure data may suffer from a positive bias, and establishing quantitative correlations between effects analysed in published scientific literature and human reproductive health outcomes is not always possible. This approach thus provides an estimate of the number of cases for which there is sufficient scientific evidence and exposure data. In addition, modelling for all substances (expect for lead) relies on air exposure data and dermal uptake is not modelled. All in all, the consequence is that the bottom-up approach represents an underestimate of the number of cases or reproductive ill health occurring as a result of occupational exposure to the relevant substances.

The bottom-up approach suggests that lead and lead compounds account for a large proportion of the total annual number of cases of reproductive ill health estimated in this study. The implication is that, although this report considers the potential benefits from the inclusion of Reprotoxic 1A/1B substances into the scope of the CMD, a large part of the burden of reproductive ill-health could be eliminated by means of lowering the Biological Limit Value (BLV) and the Binding Occupational Exposure Limit Value (BOELV) for lead under the CAD and ensuring compliance with the revised limit values.

Valuation of Burden of Ill health under the Baseline

The economic cost of reproductive ill-health, using the bottom-up calculations, are estimated at between (rounded):

- €460,000 for the 30 substances and €530,000 after extrapolation under the lowest realistic scenario; and
- €2.5 million for the 30 substances and €2.8 million after extrapolation under the highest realistic scenario.

The estimates using the top-down analysis are higher, given the higher number of cases predicted through this method. Based on the use of willingness to pay values, these are estimated at a between €9.1 and €24.3 million per annum for the geometric mean for developmental effects and between €29.7 and €79.5 million per annum for fertility and maternal effects for the geometric mean. At the maximum worst case (Scenario 1 which includes welding and taking the worst-case scenario), the figures rise to €91 million for developmental effects and €290 million for fertility and maternal effects.

Although the numbers of cases calculated under the two approaches are relatively low, the 30 substances are expected to account for around 90% of the overall risk characterisation score for all Reprotoxic 1A/1B substances that are not also Carcinogens or Mutagens 1A/1B. In addition, the top down assessment has a multiplier of 2 built into the estimates to try and account for potential worker exposures above the threshold for effects to other Reprotoxic 1A/1B substances that are not also Carcinogens or Mutagens 1A/1B. In this respect, it is important to remember that the starting point for the assessment was a review of the Classification and Labelling Inventory, which found that there were only 52 fully registered or intermediate substances with harmonised classifications as Reprotoxic 1A/1B substances that were not already Restricted or subject to Authorisation, or held classifications as Carcinogens 1A/1B and, thus, would fall under the CMD for OSH purposes.

Valuation of impacts has drawn on the use of DALYs avoided and direct and indirect cost of illness estimates for the bottom up approach and willingness to pay estimates for the top down approach. It did not prove possible to apply the DALYs approach to the top down estimates due to the number and range of developmental effects that would require consideration. The combined use of the two approaches should ensure that the end estimates are indicative of the range of health impacts.

Summary of the Policy Options

The Policy Options assessed in this report are:

Option 1- (baseline without additional guidance): No changes to EU Occupational Safety and Health (OSH) legislation and no additional OSH guidance;

Option 1 (baseline including additional guidance): No changes to EU OSH legislation, additional OSH guidance at EU level;

Option 2: Extending the CMD to all Reprotoxic 1A/1B substances;

Option 3: Extending the CMD to all Reprotoxic 1A/1B substances but providing derogations from key requirements. These derogations would be revoked for individual substances for which the absence of a threshold for reproductive effects is established by an EU scientific committee;

Option 3+: Based on the Cefic[23]/ECEG[24]/ETUC[25]/IndustriAll[26] declaration[27] - extending the CMD to all Reprotoxic 1A/1B substances, always applying requirements on substitution and closed systems, possibility of a derogation from the exposure minimisation requirement in the event of compliance with a health-based BOELV;

Option 4: Merging the CAD and CMD into a single piece of legislation and applying CMD-equivalent requirements to all Reprotoxic 1A/1B substances; and

Option 5: Merging the CAD and CMD into a single piece of legislation, applying CMD-equivalent requirements to all Reprotoxic 1A/1B substances, updating/modernising OSH terms and requirements, and introducing several add-on elements (including breaking the link between mandatory use of health surveillance and BLVs and applying a non-threshold approach to respiratory and skin sensitisers).

Further details on the Policy Options are provided in Table 1.

Table 1: Policy Options

Option	Details
O1-: Baseline without OSH guidance	No changes to EU OSH legislation but exposure may change due to other legislation and market developments. No additional guidance provided

[23] The European Chemical Industry Council
[24] The European Chemical Employers Group
[25] The European Trade Union Confederation
[26] IndustriAll European Trade Union
[27] See https://www.etuc.org/sites/default/files/press-release/file/2018-10/Joint%20Declaration%20Reprotoxics%20signed.pdf

Table 1: Policy Options	
Option	**Details**
O1: Baseline (no changes to EU OSH legislation, guidance provided)	No changes to EU OSH legislation but exposure may change due to other legislation and market developments. Provision of additional guidance on best available techniques and interpretation of the CMD/CAD
O2: R 1A/1B in CMD (no derogations)	Inclusion of R 1A/1B chemicals into the scope of the CMD with full application of the requirements in the CMD, including: - Substitution: stricter requirement than in the CAD: o mandatory whenever workers 'are or are likely to be exposed' o 'risk > slight risk' not a prerequisite - Closed system: second RMM in the hierarchy under the CMD vs. no explicit reference to closed systems in the CAD (except for intermediates); - Reduction of exposure to as low as technically feasible (minimisation requirement); - IOELVs for R 1A/1B substances would become BOELVs: IOELVs under the CAD for R 1A/1B substances would become BOELVs under the CMD; and - Record keeping: Record keeping for at least 40 years would be required for R 1A/1B substances.
O3: R 1A/1B in CMD with derogations	Inclusion of R 1A/1B into the scope of the CMD but with derogations from the substitution, closed system, minimisation and record keeping requirements, unless an EU scientific committee confirms the substance has no threshold for reprotoxic effects. CAD IOELVs for R 1A/1B substances become BOELVs under the CMD.
O3+: Cefic/ECEG/ETUC/IndustriAll Declaration: R 1A/1B in CMD with derogations	Inclusion of R 1A/1B into the scope of the CMD with the following requirements: - A Binding OELV (risk or health based) would be established for Rs; - CMD requirements on prevention (substitution, closed system) would always apply to reprotoxic substances; - If prevention were not possible, then exposure must be reduced to a) a 'safe level' (see below) or b) as low as possible (minimisation requirement); - Safe level: a) the substance has a threshold, b) there is a health-based Binding OELV (including CAD IEOLVs->CMD BOELVs), c) it is proven by exposure measurements that the BOELV is complied with; - Differentiated approach (non-threshold vs safe level) should also be applied to C/M.
O4: Merge CAD & CMD into a single directive but no modernisation	Merging the CMD and CAD into a single directive, applying CMD-equivalent requirements to R 1A/1B substances but no further changes: - This would effectively be CAD and CMD in parallel but in one document; - Old terminology: language would not be updated or modernised; - CMD-equivalent requirements would apply to CMR 1A/1B substances and CAD requirements would apply to other hazards.
O5: Merge CAD & CMD and modernise	Merging the CMD and CAD, applying CMD-equivalent requirements to R 1A/1B substances and updating/modernising OSH terms and requirements: - CMD-equivalent requirements apply to CMR 1A/1B substances and CAD-equivalent requirements apply to other types of hazardous substances; - Common terminology for substances subject to CMD-equivalent and CAD-equivalent requirements; - Terminology brought into line with REACH; and - Add on elements: a) skin and respiratory sensitisers would also be subject to CMD-equivalent requirements and b) use of BLVs as part of health surveillance would not be mandatory.

Costs of the Policy Options

No additional costs would arise under Option 1-. The guidance developed under Option 1 is expected result in some additional costs for public authorities and companies. With regard to the inclusion of Reprotoxic 1A/1B substances into the CMD, the more stringent requirements in the CMD have the potential to increase compliance costs for companies in the Member States where these requirements are presently not applied to Reprotoxic 1A/1B substances that are not also C/M 1A/1B. The cost of some of these measures, expressed as an annualised cost, has been estimated between €400 million

and €900 million, as indicated in Table 2.[28] These figures include the costs of considering and documenting the feasibility of substitution and closed systems, as well as implementing closed systems and further measures to minimise exposure.

Due to the large number of uncertainties involved in the estimation of these figures, the range should be seen as illustrative of the general order of magnitude of the potential costs rather than 'definite' estimates. In addition, some relevant compliance costs could not be monetised and, consequently, this range does not represent all the costs that would be incurred. For example, the costs of substitution and compliance with additional Binding Occupational Limit Values (BOELVs) could not be estimated. The costs of substitution are substance specific and a case-by-case examination of all relevant substances and their alternatives in all the relevant sectors/uses has not been possible within the constraints of this study. It is expected that, in some cases, the cost of substitution could be significant. It should, however, be also noted that it is possible that some Member States would take economic feasibility into account when enforcing this provision and that most companies should already be covered by the general substitution requirement in the CAD.

The costs within the range presented above are likely to arise under Options 2, 3+, 4 and 5, all of which involve the extension of the CMD to cover Reprotoxic 1A/1B substances. In the absence of scientific evaluations for all the relevant substances, it is not possible to determine which specific substances would be included into the scope of the CMD requirements under option 3. The costs of Option 3 are likely to be lower than those of Options 2, 3+, 4 and 5 but greater than under Options 1- and 1. In addition, the costs of Option 3 would be staggered as specific non-threshold substances are included into the scope of the relevant requirements over time. Option 3+ can be expected to be the most costly method of extending the CMD to Reprotoxic 1A/1B substances, since it is likely to accelerate the process of adoption of Binding Occupational Exposure Limit Values (BOELVs) for Reprotoxic 1A/1B substances that are not also C/M 1A/1B and would thus involve costs of compliance with these limits, including the need to prove compliance by means of exposure measurements for companies that are already below the thresholds for effects.

The costs of the different policy options are summarised in Table 2.

Table 2: Costs under the different Policy Options
Legend: ++++: very high costs, +++: high costs, ++: medium costs, +: limited costs, 0: no costs

Aspect ↓	Policy Option →		O1-	O1	O2	O3	O3+	O4	O5
Costs for companies (annualised cost)									
Additional OSH guidance			0	++	++	++	++	++	++
Extension of CMD to R 1A/1B	Substitution	Consideration	0	0	++ (€10-20m)	+	++ (€10-20m)	++ (€10-20m)	++ (€10-20m)
		Implementation	0	0	Potentially ++++	++	Potentially ++++	Potentially ++++	Potentially ++++
	Closed systems	Consideration	0	0	+++ (€180-260m)	++	+++ (€180-260m)	+++ (€180-260m)	+++ (€180-260m)
		Implementation	0	0	++ (€60-240m)	++	+++ (€60-240m)	+++ (€60-240m)	+++ (€60-240m)
	Exposure minimisation		0	0	+++ (€80-250m)	++	++ (less than O2, 4, 5)	+++ (€80-250m)	+++ (€80-250m)
	11 CAD Indicative OELVs -> CMD Binding OELVs		0	0	+	+	+	+	+
	Record keeping		0	0	++ (€80-140m)	+	Unknown	++ (€80-140m)	++ (€80-140m)

[28] Due to the large number of uncertainties involved in the estimation of the costs, the quantified ranges in Table 2 are illustrative of the magnitude of the potential impacts rather than definite estimates.

Table 2: Costs under the different Policy Options *Legend: ++++: very high costs, +++: high costs, ++: medium costs, +: limited costs, 0: no costs*								
Aspect ↓	**Policy Option →**	**O1-**	**O1**	**O2**	**O3**	**O3+**	**O4**	**O5**
Additional BOELVs		+	+	+	+	++++	+	+
Merging of the two directives		0	0	0	0	0	+	+
Substance-by-substance threshold vs non-threshold approach		0	0	+++	0	++	+++	+++
Modernisation of terms		+	+	+	+	+	+	Unknown
Add-on elements	Health surveillance/ Biological Limit Values	0	0	0	0	0	0	Unknown
	Non-threshold approach for sensitisers	0	0	0	0	0	0	Potentially +++
Public authorities (total cost in € million)								
EU – development of OSH guidance		0	€10m	€10m	€10m	€10m	€10m	€10m
Member States – transposition cost		0	0	€3m	€3m	€3m	€3m	€3m

The central assumption of the cost assessment is that that 2% of companies have workers potentially exposed to Reprotoxic 1A/1B substances and would thus incur some costs. This is in line with the approach of the CMD in which exposure signifies risk. The 2% estimate is based on consultation for this study and represents a reasonable worst-case scenario. A sensitivity analysis with 1% and 3% is provided in the report.

The impacts of the extension of the CMD to cover Reprotoxic 1A/1B substances to a large extent depend on the transposition and enforcement decisions taken at the Member State level – these are highly uncertain and the stringency with which the requirements would be interpreted in individual Member States cannot be predicted with any degree of certainty. In addition, the impacts of some of the policy options depend on unknown factors, such as whether a scientific body would deem certain substances to have a threshold for reproductive effects and what would be the value of a health-based BOELV. As a result, estimation of the expected costs and benefits is difficult. Therefore, the analysis in this report should be taken as merely illustrative of the general order of magnitude of the potential costs and benefits. Some of this uncertainty is captured in the ranges presented in this report but there is remaining uncertainty that could not be quantified.

Benefits of the Policy Options

No reduction in ill-health is expected under Option 1-. Increased uptake of 'best practices' under Option 1 is expected to reduce reproductive ill health but not as much as Options 2, 3, 3+, 4 and 5.

The more stringent requirements in the CMD (differences between the substitution requirements, explicit reference to closed systems and the requirement to minimise exposure, etc.) have a potential to reduce reproductive ill health in the Member States where these requirements are not yet applied to Reprotoxic 1A/1B substances. Due to the large uncertainty, the potential reduction has been estimated to be between 1 and 380 cases of reproductive ill health per year which have a total monetary value between €20,000 and €31 million annually, due to direct, indirect, and intangible costs borne by workers, their families, employers and the public sector.[29] It should be noted that some of the impacts could not be quantified suggesting that these figures are underestimates, although the assumptions adopted for the estimation of ill health reduction resulting from additional exposure prevention/reduction measures mean that the estimated reduction is likely to be an overestimate (see the uncertainty/limitations summary below). These benefits are likely to occur under Options 2, 3+, 4 and 5 which all involve an extension of the CMD to all Reprotoxic 1A/1B substances. Option 3+ is expected to be the most effective option in terms of reducing reproductive ill health since it is likely

[29] Due to the large number of uncertainties involved in their estimation, the benefits estimated in Table 3 are illustrative of the magnitude of the potential impacts rather than definite estimates.

to accelerate the introduction of BOELVs for Reprotoxic 1A/1B substances that are not also C/M 1A/1B. Reductions in ill health under Option 3 are expected to be staggered as non-threshold substances would be included into the scope of the relevant requirements one by one over time. This means that (in the near future as well as when summed up over a longer timeframe) the benefits from Option 3 are likely to be less than those from the options which involve an immediate application of the CMD requirements to Reprotoxic 1A/1B substances.

Although the bulk of the monetised benefits from avoided direct, indirect, and intangible costs of ill health would be accrued by workers and their families, employers would also benefit from reduced absenteeism, administrative simplification, level playing field across the EU, and under those options that differentiate between T and NT on a substance by substance basis also from increased efficiency and trust in the fairness of the OSH system. Public authorities are also likely to benefit from reduced healthcare and social security expenditure – these savings are included in the ranges presented above.

A comparison of the policy options for each impact category is provided in Table 3.

Table 3: Benefits of the different Policy Options *Key: ++++ substantial benefits, +++ significant benefits, ++ some benefits, + limited benefits, 0 no change.*									
Aspect ↓	**Policy Option →**	**Relevant stakeholders**	**O1-**	**O1**	**O2**	**O3**	**O3+**	**O4**	**O5**
Reduced ill health due to OSH guidance		Workers & families	0	++	++	++	++	++	++
Health benefits from extension of the CMD to R 1A/1B substances	Substitution and closed systems		0	0	++ 1-191 avoided repro cases p.a. €0.02-16m p.a.	++ Not possible to quantify but less than under O2, O3+, O4, and 05	++ 1-191 avoided repro cases p.a. €0.02-16m p.a.	++ 1-191 avoided repro cases p.a. €0.02-16m p.a.	++ 1-191 avoided repro cases p.a. €0.02-16m p.a.
	Exposure minimisation		0	0	++ 4-191 avoided repro cases p.a. €0.08-16m p.a.		++ 4-191 avoided repro cases p.a. €0.08-16m p.a.	++ 4-191 avoided repro cases p.a. €0.08-16m p.a.	++ 4-191 avoided repro cases p.a. €0.08-16m p.a.
	40 years of record keeping	Authorities	0	0	++	+	0	++	++
	11 CAD IOELVs -> CMD BOELVs	Workers & families	0	0	0	0	0	0	0
Additional OELVs for R 1A/1B substances		Companies, authorities	++	++	++	++	+++	++	++
Add-on elements (Biological Limit Values and sensitisers)		Workers and their families	0	0	0	0	0	0	+++
Reduced absenteeism		Companies	0			Included in health-related benefits (see above)			
Reduced healthcare and social sec. expenditure		Authorities	0						
Administrative simplification		Companies	0	+	++	+++	+++	+++	++++
Administrative simplification – legal coherence		Authorities	0	+	++	+++	+++	+++	++++
Administrative simplification – ease of enforcement		Authorities	0	+	++	+	++	++	+++
Level playing field		Companies	0	+	+++	++	++++	+++	+++
Fundamental rights		Workers & families	0	+	+++	++	+++	+++	+++
Modernisation of terms		Authorities, companies, workers	0	0	0	0	0	0	+++
Individual substance approach (Threshold vs Non-threshold)		Companies	0	0	Significant negative impact	++	++ (but +++ if extended to C/M)	Significant negative impact	Significant negative impact
Overall health benefits for R 1A/1B substances		***Workers & families, companies, authorities***	***0***	***+***	***+++ 1-382 avoided repro cases p.a.[1] €0.02-31m p.a.***	***++ Not quantified but less than under O2, O3+, O4, O5***	***+++ 1-382 avoided repro cases p.a.[1] €0.02-31m p.a.***	***+++ 1-382 avoided repro cases p.a.[1] €0.02-31m p.a.***	***+++ 1-382 avoided repro cases p.a.[1] €0.02-31m p.a.***

Notes: p.a.: per annum; IOELV: Indicative Occupational Exposure Limit Value; BOELV: Binding Occupational Exposure Limit Value
1: The low end of the sum of avoided cases does not take into account exposure minimisation since these benefits are highly uncertain

The uncertainties set out above for the cost assessments are also applicable to the benefits estimated in Table 3. In addition, substitution is assumed to eliminate all reproductive ill health in the relevant companies and does not take into account the characteristics of the potential substitutes – the estimates of the reduction in ill health presented in this section could thus be overestimates. Closed systems are assumed to eliminate all exposure and this is also likely to overestimate the benefits since some exposure is likely to remain during maintenance and cleaning. The modelling also assumes that any company that further minimises exposure would eliminate all reproductive ill health – this is unlikely to be the case in reality and thus the estimated reduction represents an overestimation. On the other hand, reduced exposure to the relevant substances is also likely to reduce a range of non-reproductive effects and these reductions are not included in the ranges presented above.

Market Effects

On the basis of modelled data regarding the numbers of companies that might be affected by different measures included within the policy options, the study concludes that, overall, the costs likely to be incurred represent a relatively low proportion of company turnover. As such, the effects on competitiveness, R&D, the internal market and competition and employment are likely to be limited.

However, in individual circumstances, in particular where companies engage in substitution of Reprotoxic 1A/1B substances, the impacts will be more significant, in particular in the case of SMEs. The relatively high proportion of large companies in the chemicals and other sectors using Reprotoxic 1A/1B substance would suggest that the potential might exist for companies to relocate outside of the EU, with larger companies having greater resources and, in some cases, existing operations in third countries. That being said, the relatively low proportion of turnover that the increased costs would represent under even the most burdensome of the policy options in comparison with the actual investment that might be required to transfer operations would appear to suggest that this will not be an option pursued by most companies (although some individual companies, particularly those which might be required to substitute Reprotoxic 1A/1B substances may opt to relocate).

The absence of detailed information regarding the numbers of companies that actually manufacture and use the different Reprotoxic 1A/1B substances means that it has not been possible to quantify the overall impacts at the sectoral level. As a result, the impacts at sectoral have had to be qualitatively analysed and might be subject to particular uncertainty. It is possible that companies using these substances operate in particular small or niche sub-sectors within the overall sectors analysed, and as such, might represent a more significant part of those particular sub-sectors.

Additionally, it is unknown how individual companies would respond to the changes that would arise under individual options and whilst the policy options clearly have different measures which will need to be adopted under each of the different options, lack of data regarding, for example, the number of companies currently operating at levels below IOELVs means that it is very difficult to establish which companies will undertake specific courses of action.

Comparison of the Policy Options

Due to the large number of uncertainties involved in the estimation of the costs and benefits, the quantified ranges presented in this report should be seen as illustrative of the magnitude of the potential impacts rather than definite estimates. In addition, some relevant (and potentially significant) costs and benefits could not be monetised, including benefits from reducing other types of health effects. Furthermore, the impacts of the extension of the CMD to cover Reprotoxic 1A/1B

substances to a large extent depend on transposition and enforcement decisions taken at the Member State level, and these cannot be predicted with any degree of certainty.

No change in the current costs and benefits is expected under Option 1-. Although the precise magnitude of the costs and benefits under Option 1 is uncertain (these depend on voluntary uptake of best practice measures), it can be expected that any benefits would be accrued in an efficient manner, i.e. unnecessary compliance costs for companies would be avoided.

Under Options 2, 3+, 4 and 5, the quantified costs outweigh the quantified benefits – in some cases, this difference can be quite significant. This conclusion does not change when qualitative scores and uncertainties for which there is some indication of their order of magnitude are taken into account. Option 3+ is expected to be the most effective option in terms of reducing reproductive ill health since it should lead to an earlier adoption of BOELVs for Reprotoxic 1A/1B substances that are not also C/M 1A/1B. It is, however, also likely to be the most costly option as a large number of companies would have to demonstrate compliance with the BOELVs. The costs under Option 3 are likely to be lower but, in the absence of scientific evaluations for all the relevant substances, it is not possible to determine which specific substances would be subject to CMD requirements. In addition, under Option 3, the costs and benefits would be staggered over time.

Under Options 2, 3, 3+, 4 and 5, the method of extending the CMD to cover Reprotoxic 1A/1B means that some companies would incur costs but would see no reductions in reproductive ill health since their workers are already exposed at levels below the thresholds for reproductive effects. This is a consequence of the extension of a non-threshold approach to threshold substances. The exemption from the exposure minimisation requirement under Option 3+ for companies that can demonstrate a 'safe level' of exposure would mitigate these costs but substantial costs would still be incurred in demonstrating compliance with BOELVs and due to the substitution and closed system requirements under the CMD. Option 3 avoids these consequences and, thus, is the and one, apart from the baseline options, least likely to result in unnecessary costs. However, reductions in ill health would be delayed under Option 3 as a determination by an EU scientific body would be necessary for CMD requirements to apply to non-threshold Reprotoxic 1A/1B substances. Furthermore, in the absence of scientific evaluations for all the relevant substances, it is not possible to determine which specific substances would be included into the scope of the CMD requirements.

Illustrative Case Studies

The study includes illustrative case studies for the following substances: lead and lead compounds, borates and retinol. The case studies show that, while a very large workforce is exposed to borates and retinol, they are typically exposed at very low levels (although some data limitations have to be recognised). As a result, no cases of reproductive ill health have been estimated for these substances under any of the realistic scenarios. However, due to the large number of companies, even limited costs on a per company basis due to the need to document feasibility of substitution/closed system have the potential to result in significant overall costs.

The lead case study is a good example of a relatively small occupationally exposed population (although it should be recognised that data are not available for some sectors) with good data availability with regard to exposure (biomonitoring is carried out widely and a binding BLV under the CAD and voluntary industry targets are in existence). Lead and lead compounds account for a large proportion of the annual cases of reproductive ill health predicted as arising from exposures to the 30 substances, with the implication that lowering the Biological Limit Value (BLV) for lead under the CAD could deal with large part of the burden of reproductive ill health as estimated under the bottom-up

approach. With regard to the Impact Assessment, it is of interest that there appears to be very little difference between the policy options in terms of the cost impacts on the relevant companies and the benefits that could be achieved.

The borates case study is an interesting example of a group of substances with a very large exposed workforce, albeit at very low intensities below the thresholds for reprotoxic effects. As a result, no cases of reproductive ill health have been estimated under any of the realistic scenarios. However, it is expected that additional requirements designed for non-threshold substances such as those in the CMD could result in significant compliance costs for the relevant companies. Due to the large number of companies, even limited costs on a per company basis due to the need to document feasibility of substitution/closed systems have the potential to result in significant costs. Similar observations have been made in the retinol case study.

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Glossary

Legal and Risk Management Terms	
ACGIH	American Conference of Governmental Industrial Hygienists
ACSH	Advisory Committee on Safety and Health at Work
ASA	ASA register (of occupational exposure hazards and procedures in Finland)
ANSES	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (National Agency for Food Safety, Environment and Labor, France)
BAuA	Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (Federal Institute for Occupational Safety and Health, Germany)
BLV	Biological limit value
CAD	Chemicals Agent Directive
CAPEX	Capital expenditure
CBA	Cost-benefit analysis
CFC	Closed-Faced Filter Cassette
CI	Confidence interval
CL	Liquid Chromatography
C&L	Classification and Labelling
CLH	Harmonised classification and labelling
CLP	Classification, labelling and packaging
Corr.	Corrosive
CM	Carcinogen and Mutagen
CMD	The Carcinogens and Mutagens Directive
CO-oximetry	Measure of Carboxyhaemoglobin
CPG	Gas Phase Chromatography
CR	Polychlorprene rubber
CRM	Critical Raw Materials
CSR	Chemical safety report
DALY	Disability adjusted life years
DNEL	Derived no effect limit
DRR	Dose-Response Relationship
ECHA	European Chemicals Agency
ERR	Exposure-risk relationship
ES	Selective Electrode
ENZ	Enzymatic Method
Eye Dam. 1	Eye Damage 1
F-AAS	Flame-Atomic Absorption Spectroscopy
FKM	fluorocarbon rubber
FLUO	*Fluorescence Detector*
FID	*Flame Ionisation Detector*
GESTIS	Internationale Grenzwerte für chemische Substanzenm (International limits for chemical substances)
GF-AAS	Graphite Furnace Atomic Absorption Spectroscopy
GM	Geometric mean
GSD	Geometric standard deviation
HPLC	High Performance Liquid Chromatography
HSE	Health & Safety Executive, United Kingdom
IA	Impact assessment

IARC	International Agency for Research on Cancer
ICP	Inductively Coupled Plasma Mass Spectroscopy
IFA	Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (Institute for Occupational Safety of the German Social Accident Insurance)
IMMUNO	Immunology Method
IOM	Institute of Occupational Medicine
Irrit.	Irritant
ISO	The International Organization for Standardization
LEV	Local exhaust ventilation
LOAEC	*Lowest Observable Adverse Effect Concentration*
LOD	Level of detection
LOQ	Limit of quantification
MEGA	IFA's workplace exposure database
mg/m^3	Milligram per cubic meter
MO	Optical Microscope
MS	Member States
NACE	"**n**omenclature statistique des activités **é**conomiques dans la **C**ommunauté **e**uropéenne" or the Statistical Classification of Economic Activities in the European Community
NBR	nitrile rubber
NR	Natural rubber
NIOSH	National Institute for Occupational Safety and Health
NOAEC	*No Observed Adverse Effect Concentration*
NOAEL	*No-Observed Adverse Effect Level*
OEL	Occupational exposure limit
OELV	Occupational exposure limit value
OR	Odds ratio
OPEX	*Operating expenditure*
OSH	Occupational health and safety
PAF	Population attributable fraction
PACT	(ECHA) Public Activities Coordination Tool
PBT	Persistent, bio-accumulative and toxic
PEL	Permissible exposure limit
PNEC	Predicted no effect concentration
PPE	Personal protective equipment
ppb	*parts per billion*
ppm	*parts per million*
PROC	The process categories
PV	Present value
PVC	Polyvinyl chloride
QALY	Quality-adjusted life year
RAC	(ECHA) Committee for Risk Assessment
RAR	Risk assessment report
REACH	Registration, Evaluation, Authorisation and restriction of Chemicals
Resp.	Respiratory
RMM	Risk management measure
RMOA	Risk management options analysis
RMIN	Nuclear Magnetic Resonance
SAA	Atomic Absorption Spectroscopy
SBS	Structural Business Statistics
SCOEL	Scientific Committee on Occupational Exposure Limits
SEA	Socio-economic analysis
Sens.	Sensitiser

SDS	Safety Data Sheets
Skin Corr. 1C	Skin Corrosive 1C
SME	Small and medium-sized enterprise
SMR	Standardised mortality ratio
STOT	Specific Target Organ Toxicity
SU	Sector of Use
STEL	Short term exposure limit
SUMER	Surveillance médicale des expositions aux risques professionnels (Medical Monitoring Survey of Professional Risks)
SVHC	Substance of very high concern
TLV	*Threshold limit value*
TOX	Toxicity
tpa	*Tonne per annum*
TWA	Time weighted average
WHO	World Health Organization
WTP	Willingness to pay

Health Terms	
Abortion (spontaneous)	The termination of a pregnancy. It can be spontaneous (also called miscarriage) or induced.
Adenocarcinoma	A malignant tumour originating in the glandular epithelium
Anencephaly	A neural tube defect, in which most of the brain and skull do not develop. Babies with anencephaly are usually stillborn or die shortly after birth (Rijk, van Duursen and van den Berg, 2016).
Aneuploidy	Having a chromosome number that is not an exact multiple of the usual haploid number
Ankyloglossia	Tongue-tie. Limited normal movement of the tongue, usually due to an abnormally shortened frenulum.
Anogenital distance (AGD)	The distance from the anus to the genitalia (the perineum), the base of the penis or vagina. It is used, in humans, as a non-invasive method of determining male feminisation and thereby predicting neonatal and adult reproductive disorders. This is the case because it is regulated by dihydrotestosterone, which may be disrupted by some chemicals. It is linked to both semen volume and sperm count: men with a short AGD have 7x the chance of being sub-fertile.
Asthenospermia	Asthenozoospermia. Reduced sperm motility.
Atrophy	Decrease in size or wasting away of a body part or tissue.
Axial malformations	Malformations of the axial skeleton. The axial skeleton is the part of the skeleton that consists of the bones of the head and trunk. In humans, it consists of 80 bones.
Azoospermia	Absence of spermatozoa from the seminal fluid
Cauda epididymis	Tail of the epididymis. Part of the reservoir of spermatozoa
Maxilla	The jaw or jawbone, specifically the upper jaw, which in humans for part of the nose and eye socket.
Cleft palate	Often occurs with left lip. The cleft is a gap or split in the roof of the mouth (palate), which is present at birth. It occurs because parts of the baby's face didn't join together properly during development in the womb.
Club food	One or both feet point down and inwards, with the sole of the food facing backwards. It is not painful for babies, but if untreated, it can become painful and make it difficult to walk [NHS.uk].

Corpora lutea (pl.)	Corpus luteum (sg.). Temporary endocrine structure in female ovaries, involved in the production of hormones. It is what remains of the ovarian follicle after a mature ovum has been released during ovulation. It is involved in the hormonal regulation of menstrual cycles and pregnancy.
Cryptorchidism	Undescended testes. Birth defect in which one or both of the testes fail to descend from the abdomen into the scrotum. If they do not descend spontaneously, it will be treated by a surgery called orchiopexy (Rijk, van Duursen and van den Berg, 2016).
Ectopic pregnancy	A complication of pregnancy in which the embryo attaches outside the uterus, usually in one of the fallopian tubes. Signs and symptoms include abdominal pain and vaginal bleeding.
Encephalocele	Cranium bifidium. A rare neural tube defect characterised by sac-like protrusions of the brain and membranes that cover it through openings in the skull. Caused by failure of the neural tube to close completely during foetal development.
Endometriosis	Common gynaecological disorder characterised by ectopic endometrium (presence of endometrial glands and stoma outside the uterus) causing benign endometrium-like inflammatory lesions outside the uterine cavity and is a major cause of chronic pelvic pain and infertility. Other symptoms include very heavy periods and pain in the lower back and abdomen (Rijk, van Duursen and van den Berg, 2016).
Endometrium	The mucous membrane that lines the inside of the uterus (womb).
Epididymis	A highly convoluted duct behind the testis, along which sperm passes to the vas deferens
Exencephaly	Birth defect where the brain is located outside the skull. Usually found in embryos as an early stage of anencephaly.
Fecundity	The capacity to conceive
General Cognitive Index (GCI)	Derived from the McCarthy Scales of Children's Abilities. This test is based on a wide variety of functions that are related to human intelligence. There are 18 tests in a battery that sample these different functions, 15 of which are combined into a composite score, which is known as the CGI.
Gynecomastia	Gynecomastia is an endocrine system disorder in which a noncancerous increase in the size of male breast tissue occurs. Occurs due to increased oestrogen levels.
Hydrocephalus	Condition characterised by excessive accumulation of cerebrospinal fluid in the brain. Can occur due to birth defects. Treated by surgical placement of a shunt system.
Hyperplasia	The enlargement of an organ or tissue caused by an increase in the reproductive rate of its cells, often as an initial stage in the development of cancer.
Hypogonadism	Reduction or absence of hormone secretion or other physiological activity of the gonads (testes or ovaries).
Hypoplasia	Underdevelopment or incomplete development of a tissue or organ.
Hypospadias	Penile congenital malformation, in which the urethra opens somewhere on the underneath side of the penis, instead of the tip. The urethra may remain split over a long distance. Treatment requires surgical repair shortly after birth (Rijk, van Duursen and van den Berg, 2016).
Leydig cells	Interstitial cells. Found adjacent to the seminiferous tubules in the testes. The produce testosterone and the presences of luteinising hormone (LH).
Malformation	An abnormally formed part of the body.
Mandible	Lower jaw or jawbone.

Menarche	The first occurrence of menstruation
Mental development index (MDI)	A test, designed to assess cognition through evaluation of sensory-perception, knowledge, memory, problem solving, and early language. It therefore measure a combination of early cognitive and language development.
Micrognathia	A condition in which the jaw is undersized. It is a symptom of a variety of craniofacial conditions. Also called mandibular hypoplasia. It can interfere with a child's breathing and feeding, but often corrects itself as the child grows.
Microphthalmia	Developmental disorder of the eye, in which one (unilateral microphthalmia) or two (bilateral microphthalmia) eyes are abnormally small and have anatomical malformations. In most cases, it results in blindness.
Necrospermia	Necrozoospermia. A low percentage of live and a high percentage of immotile spermatozoa in semen.
NONS	Notification of New Substances
Neural tube defects	Birth defects of the brain, spine, or spinal cord. They happen in the first month of pregnancy, often before a woman even knows that she is pregnant. The two most common neural tube defects are spina bifida and anencephaly (Rijk, van Duursen and van den Berg, 2016).
Oedema	Excess of watery fluid collecting in a cavity or tissue of the body.
Oestrus	The regularly occurring period of sexual receptivity in most female mammals.
Oestrus cycle	The recurring physiological changes that are induced by reproductive hormones in most mammalian females. Oestrous cycles start after sexual maturity and are interrupted by pregnancy. Humans have menstrual cycles rather than oestrous cycles – they have "concealed ovulation", a lack of obvious external signs to signal sexual receptivity at ovulation.
Oligospermia	Deficiency of sperm cells in the semen.
Omphalocele	Birth defect in which an infant's intestine or other abdominal organs are outside of the body, due to a hole in the naval area. The intestines are covered by only a thin layer of tissue and can be easily seen. It is repaired with surgery, although not always immediately.
Oocyte	A cell in an ovary which may undergo meiotic division to form an ovum.
Orofacial cleft	Cleft lip and cleft palate.
Ossification	Osteogenesis. The process of laying down bone material by cells called osteoblasts. Synonymous with bone tissue formation.
Ovarian cyst	A fluid-filled sac within the ovary. Most ovarian cysts are related to ovulation, being either follicular cysts or corpus luteum cysts. Many small cysts occur in both ovaries in polycystic ovarian syndrome (PCOS).
Preputial separation	Separation of the prepuce (foreskin) from the glans of the penis. It is androgen dependent, occurs around the time of puberty, and is an external sign of pubertal development in male rats.
Resorption	Disintegration and assimilation of a dead foetus into the uterus at any stage after the completion of organogenesis. Usually observed in animal experiments.
Scapula	Shoulder bone, shoulder blade, or wing bone. The bone that connects the humerus (upper arm bone) to the clavicle (collar bone).
Schistoglossia	Cleft tongue. Congenital fissure or cleft of the tongue.
Seminal vesicle	Vesicular gland, seminal glands. A pair of simple tubular glands next to the bladder of male mammals. The secrete fluid that partly composes the semen.

Seminiferous tubule	Located within the testes, they are the location of meiosis, and subsequent creation of male games, i.e. sperm(atozoa).
Sex ratio	Ratio of male to female offspring.
Sexual dysfunction	Difficulty experienced by an individual or coupe during any stage of normal sexual activity.
Spermatid	Immature male sex cell formed from a spermatocyte and may develop into a spermatozoon.
Spermatocele	Epididymal cyst. A painless, fluid-filled cyst in the long, tightly coiled tube that lies above and behind each testicle (epididymis).
Spermatocyte	A cell produced at the second stage in the formation of spermatozoa. Divides by meiosis into a spermatid.
Spermatogenesis	The process by which haploid spermatozoa develop from germ cells in the seminiferous tubules of the testes.
Spermatozoa	(pl.) Spermatozoon (sg.). The mature, motile male sex cell of an animal, by which the ovum is fertilised.
Spermiation	The process by which mature spermatids are released from Sertoli cells into the seminiferous tubule lumen, prior to their passage to the epididymis.
Spina bifida	A neural tube defect in which the foetal spinal column doesn't close completely. There is usually nerve damage that causes at least some paralysis of the legs (Rijk, van Duursen and van den Berg, 2016).
Spina bifida occulta	A mild neural tube defect, which involves incomplete formation of the neural arches of several vertebrae and is usually asymptomatic (Rijk, van Duursen and van den Berg, 2016).
Teratospermia	Teratozoospermia. Semen alteration in which there is a large number of spermatozoa with abnormal morphology. It can lead to male infertility.
Testicular dysgenesis syndrome (TDS)	A hypothesis that proposes that common reproductive disorders of newborn and adult human males may have a common foetal origin. These disorders include poor semen quality, testis cancer, undescended testicles (cryptorchidism) and hypospadias. It is theorised that TDS may be increasingly common due to environmental influences, resulting in disruption of embryonal programming and gonadal development during foetal life (Skakkebæk, Rajpert-De Meyts and Main, 2001).
Tubal pregnancy	See 'ectopic pregnancy'
Vaginal patency	The openness of the vagina.

1 Introduction

1.1 Background

As noted in the Communication on the EU Strategic Framework on Health and Safety at Work (2014-2020)[30], ensuring a safe and healthy work environment for over 217 million workers in the EU is a strategic goal for the European Commission. One of the main challenges highlighted in the Strategic Framework is the need to improve the prevention of work-related diseases by tackling existing, new and emerging risks. Occupational cancer and dealing with dangerous chemicals (including those with reprotoxic effects) in workplaces are considered to be particular priorities for occupational safety and health (OSH) policy, requiring continued effort to reduce occupational exposure to hazardous chemicals in general, and to carcinogenic, mutagenic and reprotoxic chemicals (CMR) in particular.

A range of legislative instruments are currently in place at EU level which regulate the use of CMR substances, with the objective of minimising exposures and reducing risks in the workplace. These include Directive 98/24/EC (Chemical Agents Directive, CAD) and Directive 2004/37/EC (Carcinogens and Mutagens Directive, CMD).

All reprotoxic substances are currently within the scope of the CAD and those reprotoxic substances that are also Carcinogens or Mutagens (C/M) 1A/1B are also within the scope of the CMD. However, a significant number of substances with a harmonised classification of Reprotoxic 1A or 1B are not also classified as C/M 1A/1B. As such, they are subject to less stringent regulatory requirements than those regulated under the CMD.

In Directive (EU) 2019/130[31], the European Parliament and the Council have called on the European Commission to assess the option of amending the scope of the CMD to include reprotoxic substances.

1.2 Aims of the study

The main study objective is to generate evidence to enable the European Commission to initiate policy discussions regarding the possible future amendment of the CMD in order to include in its scope Reprotoxic 1A and 1B substances or, based on a possible merger of the CMD and CAD, the necessary additional requirements that would be necessary to address risks from reprotoxic chemicals. This includes a number of specific tasks which are detailed in the Terms of Reference for the study[32].

1.3 Structure of this report

This report (Report 1) presents the outputs from the tasks that assess the baseline, i.e. estimate the incidence and/or prevalence of reproductive ill health caused by occupational exposure to chemicals and set out the current legislation and the approaches to its implementation, including voluntary industry approaches. Report 2 (separate document) presents the outputs from the tasks that assess the impacts of the policy scenarios for the amendment of the CMD or a possible merger of the CAD and CMD.

[30] See http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52014DC0332&from=EN
[31] See https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32019L0130
[32] See https://etendering.ted.europa.eu/document/document-file-download.html?docFileId=36431

Part A: The Regulatory Context and Relevant Issues

- Section A1 sets out the structure of Part A;
- Section A2 describes the different regulatory systems in place at the EU and national level; and
- Section A3 assesses the threshold/non-threshold distinction within the OSH system and its application to Reprotoxic 1A/1B substances.

Part B: Estimation of Ill health under the Baseline Scenario

- Section B1 provides a summary of the analytical approaches in this report and contextual information (strategic approaches and best practice RMMs);
- Section B2 provides the estimates of ill health derived using the top-down approach;
- Section B3 provides the bottom-up estimates of the burden of ill health; and
- Section B4 provides the economic valuation of these estimates of ill health and discusses potential future changes to this baseline.

The report is complemented with the following annexes:

- Annex 1 provides additional information on the methodology under the top-down and bottom-up estimates;
- Annex 2 provides a summary of round 1 of the consultation exercise for this study;
- Annex 3 provides further information legislation in EU and non-EU countries;
- Annex 4 evaluates the threshold/non-threshold paradigm and its applicability to reprotoxic substances;
- Annex 5 provides additional information on sensitisers (add-on element under Option 5);
- Annex 6 provides a list of the health effects considered under the bottom-up approach;
- Annex 7 deals with strategic approaches and risk management measures;
- Annex 8 gives examples of strategic and voluntary approaches;
- Annex 9 provides further information on the shortlisting process for the bottom-up assessment; and
- Annexes 10-21 provide further analysis for the 12 substance groups (30 substances) considered in detail in the bottom-up assessment.

Part A: The Regulatory Context and Relevant Issues

A1 Introduction to Part A

Part A (The Regulatory Context and Relevant Issues) has been organised as follows:

- Section A1 (this section) sets out the structure of Part A;
- Section A2 describes the different regulatory systems in place at the EU and national level; and
- Section A3 assesses the threshold/non-threshold distinction within the OSH system and its application to Reprotoxic 1A/1B substances.

The relevant annexes that complement Part A are at the end of the whole report and include:

- Annex 3 provides further information legislation in EU and non-EU countries;
- Annex 4 evaluates the threshold/non-threshold paradigm and its applicability to reprotoxic substances; and
- Annex 5 provides additional information on sensitisers (add-on element under Option 5).

A2 The EU and National Regulatory Systems

A2.1 Introduction

This section summarises the key features of the regulatory systems seeking to protect workers from risks arising from occupational exposure to reprotoxic 1A and 1B substances at the EU level, in EU Member States, non-EU EEA Countries (Norway, Iceland and Liechtenstein) and major EU trading partners.

The first part of the section focuses on the EU Regulatory system by providing a description of the overall legal framework, the key features of the OSH and chemicals legal frameworks and then a comparison of the main characteristics of the two main Directives, the CAD and the CMD.

Next, a summary analysis of the EU Member States' methods of implementation of the CAD and the CMD will be provided, followed by some insights on third countries' legislation pertaining to OSH.

Lastly, this section presents a synthesis of the findings on the national regulation of reprotoxins within the EU Member States.

A more detailed assessment of the regulatory systems may be found in Annex 3, which also comprises an overview of potential needs for interpretation of certain provisions of the CAD and CMD, as well as illustrations of the EU Member States' implementations. Additionally, this Annex summarises the provisions that EU Member States have adopted in their national legislation transposing the CAD and CMD, which go beyond the minimum requirements of the CAD and CMD with regard to risk assessment, risk management, and other measures, as well as the legal approaches to the regulation of reprotoxic substances in EU and non-EU countries.

Key findings

Based on the comparison of the key features between the CAD and the CMD, the main differences between the two Directives rest upon the following elements:

- The starting points triggering the application of the Directives;
- The prescribed Occupation Exposure Limit values;
- The level of risk considered;
- The circumstances in which substitution should be considered;
- The criteria for deciding on substitutability;
- The Risk Management Measures applicable where substitution is not required.

When looking at the EU Member States' implementation of the CAD and the CMD, the countries have broadly selected one of the following approaches for transposition:

- National measures that transpose the two Directives in two separate legal instruments (10 Member States);
- National measures that transpose the two Directives in one legal instrument (5 Member States);
- Implementation in a series of national measures (13 Member States).

Moreover, as the two Directives are of minimum harmonisation, countries may impose more stringent obligations within their national implementing legislation. While many countries have

used this opportunity to specify certain obligations under the CAD or the CMD, such as the manner in which a risk assessment should be carried out, others have extended the scope of application of their national legislation transposing the CMD, or only certain provisions of such legislation, to include reprotoxins or a broader range of chemical substances than carcinogens or mutagens.

This is notably the case of Austria, Belgium, Czech Republic, France and Sweden for example, which have extended most or all provisions of their national legislation implementing the CMD to include reprotoxins. Whereas, Finland, Germany, the UK have extended only certain provisions and therefore create a more complex situation to analysis from an implementation perspective.

Approach

Extensive consultation was carried out with the EU Member States to ensure up-to-date information, notably through two rounds of questionnaires with questions pertaining to the EU Member States' national implementation of the CAD and the CMD and the manner in which they regulate reprotoxins. Follow-up communications with certain Member States were also undertaken.

The findings in the Report are therefore based on the information provided in the responses to the questionnaires and follow-up communications. Where no response was provided, or where contradicting information was received, the following sources were used:

- Milieu/RPA report[33] from 2012;[34]
- EU Commission Study on Minimising chemical risk to workers' health and safety through substitution from 2012;[35]
- COWI/Milieu/IOM, Country Summary Reports of 2015;[36]
- Desk research for this study: country by Country Reviews for CMR update 1 January 2014.

Limitations/uncertainties

The following report is focused on the regulatory systems that have been put in place within EU Member States while implementing the CAD and CMD in order to protect workers from risks to their health arising from exposure to reprotoxic chemicals categories 1A/1B.

In view of the complexity of certain legal systems in the EU Member States, notably those where powers relating to occupational safety and health may be exercised at different levels of authority, certain limitations were necessary.

To that effect, this section does not specifically consider:

- Differences in Occupational Exposure Limit Values (OELVs) or Biological Limit Values (BLVs)

[33] DG EMPL report on "Analysis at EU-level of health, socioeconomic and environmental impacts in connection with possible amendment to Directive 2004/37/EC to extend the scope to include category 1A and 1B reprotoxic substances". Study contract VC/2010/0400.

[34] The information in Milieu/RPA (2013) has been updated to the current time and complemented with any new information that has become available. Additional new research has been included for the Member States not included at that time (Croatia), non-EU EEA Countries (Norway, Iceland and Liechtenstein) and major EU trading partners (Australia, Brazil, Canada, China, India, South Korea, Switzerland, USA).

[35] DG EMPL, Study on "Minimising chemical risk to workers' health and safety through substitution", DOI 10.2767/77360, July 2012.

[36] COWI, Milieu and IOM, "Evaluation of the EU Occupational Safety and Health Directives", individual country summaries, VC/2013/0049, June 2015.

that are established following the implementation of the CAD and CMD;
- Separate legislation that may set out the OELVs and BLVs;
- Legislation implementing Directive 92/85/EEC on Pregnant Workers;
- Legislation implementing Directive 94/33/EC on Young People at Work;
- Legislation applicable to specific substances such as lead or asbestos;
- Legislation applicable to types of exposure such as radiation;
- Additional legislation that may complement what the report identifies as the main instruments, due to the national legislative structure which may provide for the allocation of occupational safety and health competences to several authoritative levels.

When analysing national implementations of the CAD and the CMD, this report has notably looked at the technical manner in which the directives were implemented by the EU Member States, referred to as the 'typology of national measures in the EU', and how such EU Member States regulate reprotoxins. To that effect, certain categories were established. However, it must be noted that for certain countries, a clear answer may not always be achievable and depending on the data and criteria used, alternative classifications of Member States could be possible. In that regard, it is notably not always possible to draw clear line as to whether some Member States have extended the CMD requirements to R1A/B substances, and/or the extent thereof.

A2.2 EU regulatory system

A2.2.1 Description of the overall legal framework

In the EU, the safety of chemicals at the workplace is regulated by legal instruments adopted within the EU Occupational Safety and Health (OSH) legal framework, as well as under the EU chemical policy framework where legislation seeks to protect human health and the environment more generally.

The overarching EU legislation governing OSH is Directive 89/391/EEC (the Framework Directive) on the introduction of measures to encourage improvements in the safety and health of workers at work. As a framework Directive, 23 subsequent Directives have been introduced for specific matters. The four Directives which are most relevant to reprotoxic substances are:

- The Chemical Agents Directive 98/24/EC (the CAD);
- The Carcinogens and Mutagens Directive 2004/37/EC (the CMD);
- The Pregnant Workers Directive 92/85/EC (the PWD);
- The Young Persons at Work Directive 94/33/EEC (the YPWD).

Among the broader measures of the EU chemicals policy, the main legislation includes:

- The REACH Regulation (EC) No 1907/2006 (the REACH Regulation or REACH); and
- The CLP Regulation (EC) No 1272/2008 (the CLP Regulation or the CLP)

REACH and the CLP cover all chemicals that are placed on the market and not process-generated substances. Both legislative acts seek to protect human health and the environment. In doing so, they also contribute to the overall protection of workers from risks to their health arising from occupational exposure to chemicals.

A2.2.2 Key features of the OSH & chemicals legal frameworks

Directives vs Regulations

The OSH framework relies on directives adopted pursuant to Article 153 of the TFEU, which impose minimum OSH requirements. Consequently, EU Member States must transpose such Directives and may adopt more stringent measures when doing so.

By contrast, the chemicals policy framework relies on regulations to achieve the protection of human health and the environment in combination with the free circulation of chemical substances within the internal market. The relevant regulations have been adopted pursuant to Articles 191 to 193 of the TFEU and are directly applicable in the Member States.

Coexistence of the two frameworks

REACH applies "without prejudice to Community workplace and environment legislation" (REACH Recital (5)), including the Framework Directive 89/391/EEC, and thus the CAD and the CMD as well (Article 2.4 of REACH).

Whilst there are not many specific provisions seeking to ensure workers' protection within REACH and the CLP, there is no doubt that these regulations, when seeking to protect human health, also seek to protect workers. For example, REACH Recital 7 provides that "to preserve the integrity of the internal market and to ensure a high level of protection for human health, especially the health of workers, and the environment, it is necessary to ensure that manufacturing of substances in the Community complies with EU law, even if those substances are exported".

In addition, REACH also includes a specific provision related to access to information for workers (Article 35) that requires them and their representatives to be granted access by the employer to the information that is to be made available in the supply chain (mainly Safety Data Sheets) in relation to the substances and preparations that they use or may be exposed to in the course of their work.

Regulatory coverage of CM vs R substances

The CAD covers all classified substances, therefore including carcinogens, mutagens and reprotoxins of categories 1A/1B (C/M/R 1A/1B) and the CMD further covers carcinogens and mutagens of categories 1A/1B (C/M 1A/1B). The reasons for this distinction include the fact that these substances can have severe health impacts and the fact that, at the time of adoption of the CAD, scientific knowledge did not allow the setting of a threshold below which carcinogens and mutagens presented no risk. Hence, the legislator sought to control the occupational exposure to C/M 1A/1B substances using an additional legal instrument.

Reprotoxic substances are only subject to the CAD, unless they are also classified as C/M 1A/1B, in which case they fall within the scope of the CMD as well. It should be noted that a significant number of substances with a harmonised classification of reprotoxic 1A/1B (R 1A/1B) are not classified as carcinogenic or mutagenic. Additionally, many substances do not have a harmonised classification under the CLP but have been self-classified as being reprotoxic under the CLP.

By contrast, REACH and the CLP contain specific provisions dealing with CMR substances together, without distinguishing between CM and R (e.g. Article 57 REACH on Substances of Very High Concern).

- CMR 1A/1B have been prioritized for registration by the first registration deadline of 1 June 2010 if manufactured or imported above 1 ton per year per manufacturer or importer (REACH Article 23.1(a)).
- CMR 1A/1B are among the classification criteria triggering the qualification as 'substances of very high concern' under REACH (Article 57) and their possible listing in the 'Candidate List' (Article 59) and eventually in Annex XIV (Article 58) for being subject to the REACH authorization process.
- CMR 1A/1B are also subject to specific classification rules under the CLP and only information on CMR substances can be used to classify mixtures containing them (Article 6.3).
- Various restrictions apply to CMR 1A/1B with regard to their manufacturing, placing on the market and use, as established under Annex XVII of REACH.

Additionally, there are numerous legislative acts covering downstream uses which regulate CMR 1A, 1B and 2 substances, that do not distinguish between CM and R either, such as the Cosmetic Regulation 1223/2009 and the EU Biocides Regulation 528/2012.

Assessing effective control of exposure to Chemicals in the workplace[37]

In order to ensure safe conditions, either for using chemicals in the context of REACH, or with regard to working conditions in the case of the CAD or CMD, the legislation mandates the use of tools that define exposure limits for humans. On the one hand, the CAD and the CMD prescribe Occupational Exposure Limits (OELS), referring to the airborne concentration of harmful chemical agents. On the other hand, under REACH, Derived No Effect Levels (DNELs) must be adopted are refer to the levels of exposure to a substance above which humans should not be exposure. While the values are used to characterise the risk and determine potential risk management measures (RMM), there are key differences among the two.

OELs are established at EU and national level, generally supported by expert independent scientific committees which consider all available scientific information, and complemented by information on exposure monitoring. Generally, OELs only considered the inhalation route of exposure, although they may indicate that another route of exposure is important. There are two different types of OELs at the EU level. First, Indicative Occupational Exposure Limit Values (IOELVs), which are health-based limits typically established for substances for which it is possible to set a threshold or a no effect level. Prior to adoption of an OEL, the European Commission's Scientific Committee for Occupational Exposure Limits (SCOEL) will perform an assessment of scientific information, taking into account the availability of measurement techniques. Once an OEL has been set at the EU level, Member States will have to introduce a national OEL, that must take into account the EU limit value. The second type of EU level OEL, is Binding Occupational Exposure Limit Values (BOELVS) that take into account socio-economic and technical feasibility factors in addition to the factors considered for IOELVs. These values aim to provide a minimum level of protection for workers at the Community level. Where BOELs exist, Member States will have to establish a national OEL based on, but not exceeding, the EU limit value. Whether an employer will have to comply with national OELs will depend on the legislation of the relevant Member State(s) and compliance with OELs may be monitored by measuring the concentration of the concerned chemical(s) in the air of the work environment.

DNELs are non-binding levels introduced by REACH and formulated by registrants (manufacturers and importers) notably as part of their REACH registration of chemical substances. They are derived for all relevant routes of exposure but only when a chemical safety assessment (CSA) is required, i.e. for

[37] See the Commission's 'Interim Guidance for National Labour Inspectors on how to use Occupational Exposure Limits (OELs), Derived No Effect Levels (DNELs) and Derived Minimal Effect Levels (DMELs) when assessing effective control of exposure to Chemicals in the workplace', SLIC WG CHEMEX, November 2015.

production/import volumes of at least ten tonnes per year. The levels are established according to a methodology set up by ECHA that differs from the methodology used by SCOEL. The CSA and the DNELs will be documented in the Chemical Safety Report (CSR) and the extended Safety Data Sheet (eSDS). Additionally, for chemical substances that do not have a threshold and for which it is therefore impossible to set a DNEL, REACH provides the possibility to set a Derived Minimal Effect Level (DMEL) rather than a DNEL, which is a reference level considered to be of very low concern. In such cases, the conditions in the exposure scenario for safe use are based on a qualitative assessment.

OELs and DNELs or DMELs co-exist and may sometimes apply simultaneously to certain work activities. DNELs are often lower than OELs and although the values are not interchangeable, REACH registrants can use an OEL, where it exists, as a DNEL for the inhalation route. When a DNEL is lower than an OEL, the RMM to meet the DNEL should nevertheless ensure that the OEL is also achieved. If it is the other way around, i.e. the DNEL is higher than the OEL, chemical users subject to OSH legislation, are required to ensure that exposure is controlled below the OEL. Lastly, if both the DNEL and the OEL are the same, provided that the RMM are effective at controlling exposure below the DNEL, they will also control the level below the OEL. However, the RMM that are set out based on the DNEL will not always allow for an employer to fulfil his RMM obligations under the OSH legal framework. Thus, the employer will also have to assess whether the RMM ensure compliance with his OSH duties.

The CAD and the CMD, within the OSH legal framework

The CAD sets out minimum requirements for the protection of workers from risks to their safety and health arising, or likely to arise, from the effects of chemical agents that are present at the workplace or as a result of any work activity involving chemical agents. Reprotoxic chemicals are covered by the CAD's broad scope of application and can present two groups of effects:

3. Effects on sexual function and fertility; and

4. Effects on the development of the foetus or offspring (developmental toxicity).

Among employer requirements under the CAD, figures the obligation to determine whether any hazardous substances are present at the workplace and assess any risk to the safety and health of workers. This assessment will notably take into account OELs that have been adopted under the CAD and whether such limit values are respected at the workplace. Based on the results of the risk assessment, employers must take any necessary preventive measures and/or eliminate or reduce the risks to a minimum, following a hierarchy of prevention and risk management measures.

The CMD aims to protect workers against health and safety risks from exposure, or likeliness thereof, to carcinogens or mutagens at work but reprotoxins may indirectly fall within the scope of the CMD if they are also C/M 1A/1B.[38] The CMD requires employers to assess any risk to workers' health or safety and ensure that the binding limit values in Annex III are not exceeded. They must also apply a range of prevention measures whenever carcinogens or mutagens are used as the workplace and replace the substances in so far as technically possible or reduce exposure to as low as level as possible, according to the hierarchy of risk management measures.

Next to the CAD and the CMD, two other Directives regulating reprotoxins were mentioned above. The PWD and YPWD are complementary to the CAD and CMD and aim to protect the health and safety of workers that are at particular risk, at their workplace.

[38] See https://osha.europa.eu/en/legislation/directives/directive-2004-37-ec-indicative-occupational-exposure-limit-values.

In that respect, the PWD aims to protect women, when pregnant, having recently given birth and/or breastfeeding. The Directive sets out a non-exhaustive list of activities liable to involve a specific risk for such women and that require employers to perform a risk assessment, based on the Guidelines drawn up by the Commission. Where such assessment reveals a risk to the safety or health of the concerned women or an effect on their pregnancy or breastfeeding, employers must take action to avoid the risk. Certain activities are specifically prohibited for such workers. Furthermore, the PWD lays down minimum requirements for maternity leave and employment rights for women that are pregnant, have recently given birth and/or are breastfeeding.

The YPWD, aims to establish minimum requirements for the protection of young people at work, i.e. people under the age of 18. The Directive instructs Member States to take the necessary measures to prohibit work by children and ensure that the minimum employment age is not lower than 15 years old. When young people are at work, their working conditions must be adapted to their age and Member States shall ensure that they are protected from any specific risks to their safety, health and development linked to their age. To that effect, certain categories of work are prohibited to young people, including for example, work involving exposure to CMRs. Further work modalities are specified in the Directive, which also allows Member States to adopt exceptions for specific types of work. The measures set out in the Directive are to be implemented by employers, prior to the young people starting work and on the basis of a comprehensive risk assessment of the hazards to young people due to their work.

A2.2.3 Comparison of the key features of the CAD and the CMD

The key issue for the analysis under this study are the differences between the legal regimes relevant to substances that are only Reprotoxic 1A/1B and are thus only subject to the CAD, and substances that are C/M 1A/1B or both Reprotoxic 1A/1B and C/M 1A/1B and are thus also subject to the CMD. The following table summarizes the provisions of the CAD and the CMD in a comparative way to present the differences between the provisions of both Directives. Based on the observations stemming from the table, this section will then focus on the main elements distinguishing the CAD and the CMD.

Table A2-1: Differences between the CAD and CMD

Area	Chemicals at Work Directive (CAD)	Carcinogens and Mutagens Directive (CMD)
General provisions		
Legal basis	Article 16.1 OSH Framework Directive, minimum requirements	Article 16.1 OSH Framework Directive; minimum requirements
Scope	▪ Hazardous chemicals present or may be present at the work place (Art. 1.2 & 2.(b)) ▪ Reference to the CLP Regulation (Art.1.2 & 2.(b)(i)) ▪ Carcinogens: more stringent requirements in specific legislation prevail (Art.1.3)	▪ Activities where workers are or are likely to be exposed to carcinogens or mutagens (CM) as a result of their work (Art.3.1) ▪ Reference to the CLP Regulation and/or substance, mixture or process (or released by a process) listed Annex I to CMD (Art.2.a)
Employer obligations		

Table A2-1: Differences between the CAD and CMD		
Area	**Chemicals at Work Directive (CAD)**	**Carcinogens and Mutagens Directive (CMD)**
Risk assessment[39]	Determine whether hazardous chemicals are present at the work place (Art.4.1) If yes, perform a risk assessment (Art.4.1)	Determine whether workers are exposed or likely to be exposed to CM as a result of their work (Art.3.1) If yes, perform a risk assessment → determine the exposure & RMM
Prevention/ reduction of occupational risks[40]	If activity involves hazardous chemical agents: General preventive measures or Art. 6(1) and 6(2) of **Dir.89/931** (Art. 5.1) 'Risks' shall be eliminated/reduced to a min. through: • List of General preventive measures in Art. 5.2 (Art. 5.2) If 'slight risk' is identified, because of quantities of chemical present: ▪ General preventive measures of Art. 6(1) and 6(2) of Dir.89/391; ▪ General preventive measures of Art. 5.2 → IF sufficient to reduce risk ➔ No other measures (Art. 5.4) If risk is identified (>'slight risk'): (Art. 5.3) • Comply with hierarchy for further RMM: 1) Substitution of the chemical 2) IF the nature of the activity does not permit risk to be eliminated by substitution: → Reduction of the risk to a min. by applying protection and prevention measures in the following order: – designing processes, controls, using adequate equipment; – collective protection measures at the source of the risk; – individual protective measures:(Art.6.2 – 6.6) ▪ Implement provisions to deal with accidents, incidents and emergencies (art.7)	Reduce the use of CM substances at the place of work, in particular by replacing it, IF technically possible (Art.4.1) If replacement not technically impossible: ▪ Comply with hierarchy for RMM: ▪ Closed system; ▪ IF closed system technically impossible: → Reduction of the level of exposure as low as technically possible (Art.5.2&5.3) Wherever a CM is used: Implement mandatory list or general prevention measures (all provided in Art. 5.5) ▪ Limitation of the quantities of CM at the place of work; ▪ Keeping the number of workers exposed/likely to be exposed to as low a level as possible; ▪ Designing processes, controls, using adequate equipment; ▪ Evacuation of CM at source; ▪ Collective protection measures at the source of the risk; ▪ Individual protective measures; ▪ (…)

Table A2-1: Differences between the CAD and CMD		
Area	**Chemicals at Work Directive (CAD)**	**Carcinogens and Mutagens Directive (CMD)**
	▪ Implement health surveillance measures where appropriate (art.10 & 6.3)	
Accidents, incidents and emergencies **Called 'unforeseen exposure in CMD'**	▪ If risk is identified (>'slight risk'): – Prepare action plans to deal with accidents, incidents and emergencies (Art.7.1) – In the event of accident, incident or emergency: ✓ Mitigate the effects and inform the workers (Art.7.2) ✓ Provide PEE to workers in the affected areas (Art.7.3) ✓ Provide warnings & communicate on the increased risk for health and safety (Art.7.4) Provide information on emergency arrangements: list (Art.7.5)	▪ Inform workers (Art.7.1) Permit access only to workers who are essential to carry the repairs and other necessary work, equipped with PPE (Art.7.2)
Information and training[41]	▪ Provide workers and/or their representatives with relevant training, data and information; list applies in addition to Framework Regulation (Art.8)	▪ Provide workers and/or their representatives with relevant training, data and information; list provided (Art.11&12) ▪ Consultation of workers for the implementation of CMD (Art.13)
Health surveillance (HS)[42]	▪ If risk is identified (>'slight risk'): – Cases where HS is required: based on exposure, likelihood of disease, etc.); compulsory if BVL (Art.10.1) – Techniques for detection of diseases (Art.10.1) – Health and exposure records (Art.10.3) ▪ If disease of a worker information, review safety assessment, search advise, continue HS (Art.10.4)	▪ If risk is identified: – For workers at risk based on the risk assessment → compulsory HS in compliance with national laws (Art.14.1) – Surveillance before and after exposure (Art.14.2) – Health and exposure records (Art.14.4) ▪ If disease/abnormality of a worker → doctor or other authority may require HS for other workers
Hygiene and individual protection	N/A	Comply with list in Article 10: ensure that no eating, drinking, smoking in C&R areas; protective clothing; storage and washing facilities; etc.
Prohibited activities	Article 9 and Annex III (prohibited substances)	N/A
Occupational limits		

Table A2-1: Differences between the CAD and CMD		
Area	**Chemicals at Work Directive (CAD)**	**Carcinogens and Mutagens Directive (CMD)**
Occupational exposure limits (OEL)	IBOELV: MSs must establish national OEL 'taking into account' the EU value BOELV: MSs must establish corresponding national binding OEL ≤ EU value	▪ Only BOELVs: MS must establish a corresponding national binding OEL ≤ EU value ▪ Requirement that employers comply with such OEL
Biological limit values (BLV)	MSs must establish corresponding national binding BLV ≤ EU value	N/A

A2.2.4 Starting points of the Directives

The first major difference between the CAD and the CMD is the starting point of each Directive, the element triggering their application.

According to article 1.2 of the CAD, the requirements set out in this Directive are applicable "where hazardous chemicals are present or may be present at the workplace". This creates a broad scope of application corresponding to the goal of the CAD, laid out in article 1.1, which is "the protection of workers from risks to their safety and health arising, or likely to arise, from the effects of chemical agents present at the workplace or as a result of any work activity involving chemical agents". The CAD specifies in article 1.3 that its provisions are applicable without prejudice to more stringent/specific measures taken under the CMD.

The CMD also aims to "protect workers against risks to their health and safety" under article 1.1 of the Directive. It is further specified that the CMD aims at the "prevention of such risks, arising or likely to arise from exposure to carcinogens or mutagens at work". The requirements of the CMD apply accordingly and will concern, based on article 3.1, activities in which workers are exposed or likely to be exposed to carcinogens or mutagens as a result of their work.

From the above, while the CAD is triggered by the presence of hazardous chemicals at the work place, the CMD is triggered by a narrower scope of application, that is when workers are exposed or likely to be exposed to carcinogens and mutagens. Indeed, there may be situations, such as when chemicals are used only in closed systems, where the workers are not exposed or likely to be exposed, but chemicals are nevertheless present at the work place.

When the relevant chemical substances are within the scope of either Directive, employers are required to perform a risk assessment and based on the outcome, implement appropriate and effective Risk Management Measures ('RMM') (Art. 4 CAD, Art. 3 CMD).

OELs for chemical substances and 'de minimis' obligations

Both Directives require the establishment of limit values for occupational exposure of workers to certain chemical substances by inhalation and in relation to a specified reference period. However, there are two differences between the CAD and the CMD with regard to OELVs.

Firstly, the CAD foresees the adoption of IOELVs, BOELVs and BLVs (Art. 3), whereas the CMD only envisages BOELVs, set out in Annex III to the Directive.

Secondly, under the CAD, where the health-based OEL is respected within the place of work, it is assumed that the risk has been eliminated and employers will not have to adopt additional risk management measures. However, if the OEL has been exceeded, the employer must take immediate steps to remedy the situations, by adopting preventive and protective measures, which take into account the nature of the limit (Article 6.3,§2). The CMD imposes stricter obligations. It states not only that "exposure shall not exceed the limit value of a carcinogen as set out in Annex III" (Article 5.4) but also requires employers to continue to reduce exposure[43] to as low as level as technically possible, even where the OEL is respected. Therefore, the CMD imposes a '*de minimis'* obligation with regard to exposure, which does not exist under the CAD.

Level of risk considered

The results of the risk assessment will determine whether, and if so which, measures ought to be implemented by the employer. To that effect, a significant difference is noted between the CAD, where a distinction is made between two levels of risk, and the CMD where this distinction does not exist.

The CAD distinguishes between (i) situations where the risk assessment reveals a 'slight risk' to the safety and health of workers and (ii) situations where the risk assessment reveals a 'risk', and implicitly iii) where the risk assessment concludes there is no risk.

In accordance with article 5.4, where only a 'slight risk' has been revealed, the application of general preventive measures set out in articles 6(1), 6(2) of the Framework Directive 89/391 and those set out in article 5.2 of the CAD could be enough. If such general preventive measures are sufficient to reduce the slight risk, then there is no requirement to take further measures. We note that the CAD qualifies the slight risk "because of the quantities of a hazardous chemical agent present in the workplace". As discussed below, there is a need for interpretation to determine whether other considerations can also be taken into account to quantify the risk.

Where the risk assessment reveals a 'risk', which by deduction is higher than a 'slight risk', further measures must be applied to eliminate or reduce such a risk. Article 5.3 specifies that these additional measures are those set out in articles 6, 7 and 10 of the CAD.

To the contrary, the CMD provides no distinction between different levels of risk that could be revealed in the risk assessment. Arguably, since the scope of the CMD requires that workers are exposed, or likely to be exposed, and since carcinogens and mutagens are by definition 'hazardous' substances', there is always some level of residual risk when there is exposure to carcinogens or mutagens at the work place. Consequently, it could be held that the risk assessment to be conducted does not seek to determine 'whether' there is a risk but the degree of risk that is present or expected. Nonetheless, certain employer obligations are explicitly subject to the risk assessment having revealed a risk, such as those listed in article 6.

The absence of a distinction between levels of risk, renders the CMD more stringent than the CAD, which offers a lighter set of obligations incumbent on the employer where the risk assessment only reveals a 'slight risk'.

When is substitution to be considered?

Substitution (also called 'replacement') is a key RMM under the CAD and the CMD but there are important differences between the two Directives. As a general remark, the CAD is more specific

[43] In the case of C/M substances which the CMD treats as non-threshold substances, exposure signifies risk.

regarding the situations in which substitution should be considered, whereas the drafting of the CMD provisions leaves room for potential interpretations. This is discussed further in this section.

There are two cases in which the CAD requires substitution to be considered:

5. Where there is a risk higher than a slight risk (Article 5.3 CAD), article 6.2 of the CAD requires substitution as the preferential measure for eliminating or reducing the risk 'to a minimum';

6. Where there is a slight risk (Article 5.4 CAD) and the general preventive measures taken in accordance with articles 5.1 and 5.2 are not sufficient to reduce the slight risk, without having to reduce it 'to a minimum'. Indeed, specific protective and prevention measures, including substitution, also apply in cases of slight risk, if the general preventive measures are not sufficient to reduce the slight risk. In that case, the risk must be eliminated or reduced to a minimum through further measures.

Under the CMD, there are two main provisions where 'replacement', i.e. substitution, is mentioned. The first is article 4.1, which refers to substitution as a particular method that employers should apply to reduce the use of a carcinogen or mutagen at the work place. The second provision referring to substitution is article 5.1-2, which starts by stating that where a risk is revealed by the risk assessment, workers' exposure must be prevented. The next paragraph states that where substitution is not technically possible, a closed system should be used. We also note that the scope of the CMD under article 3.1 requires that there is or is likely to be exposure to a carcinogen or mutagen. This is in line with the fact that, at the time of adoption of the CMD, the prevailing scientific opinion was that C/M substances have no threshold and, as a result, no level of exposure, however small, can be safe. This means that whenever an activity falls within the scope of the Directive, there is a residual risk, unless the substance is replaced with another substance that is not C/M or a completely closed system is used.

As a worst-case scenario in relation to the costs for companies, the analysis in this study is based on the interpretation that the CMD requires substitution to be considered in any case where workers are or are likely to be exposure to a carcinogen or mutagen.

Nonetheless, the circumstances triggering substitution as an RMM are different under the CMD than under the CAD, since the lighter set of obligations that the CAD offers where there is only a slight risk does not explicitly include the obligation to consider substitution as an RMM. This means that substitution will not necessarily be considered as an RMM each time a hazardous chemical agent is 'present' or 'used' at the workplace under the CAD. Such consideration is dependent on the level of risk that is revealed in the risk assessment. To the contrary, under the CMD, once an activity falls within its scope, substitution is considered as an RMM at least in all cases where there is exposure, or likeliness thereof, and thus whatever the level of risk revealed in the risk assessment.

In practice, most Member States have used a similar wording to the CMD when implementing the provisions on substitution. However, certain Member States have adapted the language of the CMD, such as Belgium for example, that explicitly requires the results of the risk assessment to reveal a risk for substitution to be considered.

What are the criteria for deciding on substitutability Once substitution is to be considered as a RMM under either Directive, it must be verified whether substitution must be applied. Both the CAD and CMD include wording reflecting circumstances that may relieve employers from the obligation to substitute. Noticeably, different terms are used to that effect in both Directives.

The CAD requires substitution in article 6.2 "where the nature of the activity permits the risk to be eliminated by substitution". It is up to the employer to evaluate whether the nature of his activity allows for substitution and in doing so, the employer must have regard to the risk assessment carried out.

Under the CMD, article 4.1 requires substitution "in so far as is technically possible". This condition is repeated throughout the hierarchy of RMM and must also be evaluated by the employer. The CMD further specifies that the authorities can request the employer to submit the findings of his investigation. This is not provided in the CAD although one could anticipate that national authorities may foresee the right to request such information under their national laws, as set out in the Czech Republic and Denmark.

It appears that certain Member States have refined the implementation of the substitution requirement by adding criteria. For example: In Austria, substitution is required if the same result can be achieved (by the alternative). In Finland, substitution is required when technically feasible and 'reasonably practicable'. In Denmark, Germany and the UK, economic considerations may be taken into account.[44] Germany also requires detailed documentation including reasons for decisions against substitution to be provided to enforcement bodies on request.

If substitution is not required, what other RMMs apply?

The measures that ought to be taken when substitution is not required vary between the Directives and this may notably be linked to the different objectives the Directives pursue. Indeed, whereas the CAD aims to minimise risks, the CMD aims to minimise exposure. To achieve such goals, the Directives do not require to same RMMs to be implemented when substitution is not possible.

Article 6.2 of the CAD sets out the protection and prevention measures to take in such case and specifies that their application should be consistent with the risk assessment. In that respect, the following measures must be taken in hierarchal order to ensure that the risk is reduced to a minimum:

a) Design appropriate work processes and engineering control and use of adequate equipment and materials to avoid or minimise the release of hazardous chemical agents which may present a risk;
b) Application of collective protection measures at the source of the risk (ex: adequate ventilation and appropriate organizational measures);
c) Where exposure cannot be prevented by other means, application of individual protection measures, including personal protective equipment (PPE).

According to the provisions of the CMD, where substitution is not technically possible, articles 5.2 and 5.3 require two other measures to be taken in hierarchal order and in so far as technically possible:

a) Ensure that the carcinogen or mutagen is manufactured and used in a closed system;
b) Ensure that the level of exposure of workers is reduced to as low a level as 'technically possible'.

While these two sets of RMM measures are different, those set out under the CAD also figure among the list of measures that apply under the CMD "wherever a carcinogen or mutagen is used" (Article 5.5), namely:

[44] Consultation for this study.

a) limitation of the quantities of a carcinogen or mutagen at the place of work;
b) keeping as low as possible the number of workers exposed or likely to be exposed;
c) design of work processes and engineering control measures so as to avoid or minimise the release of carcinogens or mutagens into the place of work;
d) evacuation of carcinogens or mutagens at source, local extraction system or general ventilation, all such methods to be appropriate and compatible with the need to protect public health and the environment;
e) use of existing appropriate procedures for the measurement of carcinogens or mutagens, in particular for the early detection of abnormal exposures resulting from an unforeseeable event or an accident;
f) application of suitable working procedures and methods;
g) collective protection measures and/or, where exposure cannot be avoided by other means, individual protection measures;
h) hygiene measures, in particular regular cleaning of floors, walls and other surfaces;
i) information for workers;
j) demarcation of risk areas and use of adequate warning and safety signs including 'no smoking' signs in areas where workers are exposed or likely to be exposed to carcinogens or mutagens;
k) drawing up plans to deal with emergencies likely to result in abnormally high exposure;
l) means for safe storage, handling and transportation, in particular by using sealed and clearly and visibly labelled containers;
m) means for safe collection, storage and disposal of waste by workers, including the use of sealed and clearly and visibly labelled containers.

Accordingly, the CMD requires more RMM to be applied when substitution is not possible than the CAD.

We also note that the requirement of a closed system, which is specifically consolidated in the CMD, is not a measure which is listed under the CAD, except for prohibited substances that are intermediates (Art.9). In practice, this requirement is perceived as very stringent and unique to the CMD. However, it could be argued that such systems could fall under article 6.2(a) of the CAD, within the meaning of 'appropriate work processes' and/or 'engineering controls'. If so, closed systems could be considered as the second RMM within the hierarchal order, in the event that the nature of the activity would not permit substitution to eliminate the risk. This is further supported by the Guidelines on the CAD where closed systems are listed as processes or installations which can be used to reduce risk and are considered a "good solution where chemical agents with a high or average hazard rating are involved".[45]

Consequently, the CMD requires additional measures to be implemented as RMMs than under the CAD, including the stringent obligation to set up a closed system where substitution is not possible.

A2.2.5 Need for interpretation in the CAD and the CMD

Based on the above analysis, certain provisions and wordings in the CAD and CMD could benefit from greater coherence and/or guidelines refining the interpretation that is to be given. Such actions could ensure a more uniform implementation and enhance industry compliance.

We also note that a majority of Member States have responded in favour to the adoption of additional guidance at the EU or national level to aid the interpretation of the OSH legal framework and/or setting out the 'best available techniques' for preventing or reducing exposure to relevant substances in different industry sectors. More specifically, the reasons behind the Member States' positions

[45] Guidelines on the CAD, p.30, 33.

included the obtaining of a better harmonisation of protection levels of workers throughout the EU and improving the practical implementation of regulatory provisions.

Therefore, the object of the following section is to addresses certain provisions which may raise such a need for interpretation.

The implementation of substitution

In 2012, the need for further guidance regarding substitution was already identified as a key measure to enhance the use of substitution.[46] It was underlined that the existing guidance at that time, were not practical or easy to implement, particularly for SMEs. We note that the current Practical Guidelines on the protection of the health and safety of workers from the risks related to chemical agents at work (Guidelines on the CAD), date back to 2005.

For smaller enterprises, substitution was perceived as far too complex a process considering the limited knowledge and capacity they can devote to systematic risk reduction. In that respect, the main barriers that were mentioned at the time were the interpretation of hazard data given in SDS, the risk assessment itself and the control of the effectiveness of the assessment. Many EU workplaces concluded that risk assessments should be made easier and more accessible by providing guidance on substitution's fundamentals, i.e. basic components of hazard identification and the inclusion of exposure potential estimation and risk assessment in a same document. Specifications with regard to risk assessments was also suggested by Member States in their consultation responses, as an element that should be included in further guidance.

Under the CAD

Characterization of a risk as 'slight'

Where the CAD provides a distinction between a 'risk' and a 'slight risk', in article 5.4, further guidance on the interpretation of the term 'slight risk' could be useful. The characterization of a risk as 'slight' is a question of proportionality based on a qualitative approach. However, the provision only specifies that a slight risk to workers' safety and health is "due to the quantities' of a hazardous chemical agent present in the workplace". Furthermore, in practice, it has been mentioned that the distinction of risks and subsequent applicable obligations has not been based on the provisions of the CAD and whether the risk is 'slight' or not but rather on common sense, i.e. risks that employers deem to be better dealt with through other measures than substitution. Indication of reference quantities that may be used, such as OELs, or non-exhaustive criteria could help guide employers towards a more consistent characterization of risks as 'slight'.

The Guidelines on the CAD may provide some insight for employers. A brief definition of a risk is provided as "the likelihood that the potential for harm will be attained under the conditions of use and/or exposure". However, these guidelines are primarily intended to assist Member States and are not legally binding. It must also be noted that the general character of the Guidelines on the CAD does not take into account the specificities of Member States' national legislation. Consequently, they may not be the ideal instrument for employers, which may already be confronted with the costs of having to abide with the various implementations of both Directives, in which case the potential additional expense linked to assessing the Guidelines on the CAD may not be conceivable. The most useful Guidelines are likely to be those intended for employers, easy to use and redacted by the national

[46] EU Commission Study Minimising chemical risk to workers' health and safety through substitution from 2012.

authorities. In that respect, the UK for example, adopted practice guidelines which are integrated into its legislation but few countries have done the same.

Article 5.4 of the CAD includes another element pertaining to the characterization of a risk as 'slight', which may benefit from interpretation, whereby it mentions that in case of a 'slight risk', further RMM do not apply where the general preventive measures of articles 6(1), 6(2) of the Framework Directive 89/391 and article 5.2 of the CAD are "sufficient to reduce that risk". Here again, there is no indication as to when a risk is to be deemed 'sufficiently' reduced to avoid the triggering of additional measures, including the need to consider substitution. Further information on the degree to which the slight risk must be reduced in order to qualify as 'sufficient' could be useful. In the event that 'any' reduction, i.e. the slightest reduction of the slight risk, would be sufficient, this could be specified.

Substitution as a preventive measure?

As set out above, based on article 5.3, 5.4 and 6 of the CAD, substitution as an RMM should be considered either when there is a risk higher than 'slight', or when the risk is 'slight' but the general preventive measures were not sufficient to reduce such risk. However, the Guidelines on the CAD further consider that substation should be considered as a preventive measure and specify that substitution is at least 'desirable', even when the risk is slight, based on two arguments.

First, since article 5.1 of the CAD, makes a reference to article 6(2) of the Framework Directive 89/391, where 6(2)(a) states 'avoiding risks' as one of the general principles of prevention, the Guidelines on the CAD deduce that "risk elimination (i.e. substitution) is actually the first principle for prevention".[47] However, we understand that substitution could also likely fall under 6(2)(f), which sets out "replacing the dangerous by the non-dangerous or the less dangerous" and that neither article 6(1) nor 6(2) set out a hierarchal order within the general principles.

Second, where article 5.2 of the CAD states that: "risks (...) involving hazardous chemical agents shall be 'eliminated', the Guidelines on the CAD establish that: 'the risk due to work involving a hazardous chemical agent is eliminated when the agent disappears. It is therefore desirable to substitute this with another chemical agent or process (...)".[48]

We note that the potential reference to substitution under article 6(2) of the Framework Directive 89/391 is very general and the reference under article 5.2 is not explicit. Additionally, under this interpretation, substitution would be more imperative where there is a slighter risk than when there is a higher risk. This interpretation would also render the CAD almost as stringent as the CMD, whereby substitution would have to be considered in all cases where a risk would be revealed by the risk assessment. In practice, this is not the understanding that seems to be retained by employers, who perceive substitution as a requirement which is more stringent under the CMD.

This demonstrates that there might be a need for interpretation with regard to the circumstances under which substitution should be understood as having to be considered as a preventive measure, under the CAD.

Under the CMD

Consideration of substitution

The main need for interpretation within the CMD pertains to the situations triggering the obligation for employer to consider substitution. This issue was referred to earlier in this section and is

[47] Guidelines on the CAD, p.19.
[48] Guidelines on the CAD, p.22.

articulated around the interpretation to be given to the scope of the CMD laid out in article 3.1, and the provisions in which substitution is brought up, i.e. article 4.1 and 5.2. In that respect, the main question is whether the prior identification of a risk in the risk assessment is required in order to apply substitution, or if substitution must be considered in all cases where a carcinogen or mutagen is used, and/or only subject to workers being exposed or likely to be exposed to such carcinogens or mutagens. The various possible interpretations stem from the following articles:

First, Article 4.1, which states the following:

> *"The employer shall reduce the use of a carcinogen or mutagen at the place of work, in particular by replacing it, in so far as is technically possible, by a substance, preparation or process which, under its conditions of use, is not dangerous or is less dangerous to workers' health or safety, as the case may be".*

The absence of any reference to the disclosure of a risk in the risk assessment, may lead Member States to consider that substitution must be considered by employers in any case where a carcinogen or mutagen is used.

Second, Article 5 is drafted in two paragraphs stating that:

> *1. "Where the results of the risk assessment (...) reveal a risk to workers' health or safety, workers' exposure must be prevented".*
>
> *2. "Where it is not technically possible to replace the carcinogen or mutagen (...), the employer shall ensure that the carcinogen or mutagen is, in so far as technically possible, manufactured and used in a closed system".*

The latter paragraph, setting out the second RMM to apply where substitution is not possible, i.e. a closed system, does not explicitly mention the prior identification of a risk following the risk assessment, unlike the first paragraph of the same article, which clearly states that such prior revelation of a risk is a pre-requisite to preventing exposure. However, the measures to take in order to 'prevent' exposure are not identified. Because the second paragraph sets out the requirement of a closed system, where substitution is not technically possible, there is room for interpretation as to whether this means that substitution and the following RMM are to be considered as measures to 'prevent' exposure and therefore, whether such measures are subject to the prior identification of a risk. If so, then substitution is could be interpreted as having to be considered where the risk assessment reveals a risk to workers' health or safety.

Nonetheless, in both cases, the scope of the CMD, laid out in article 3.1, should be considered as well. Accordingly, the Directive is only applicable to employer activities in which workers are exposed or likely to be exposed to carcinogens or mutagens, as a result of the work they carry out. Therefore, it could be considered that because carcinogens or mutagens are intrinsically hazardous, the requirement that there must be exposure to such substances, or a likeliness of exposure, could mean that a residual risk always exists once activities fall under the scope of the CMD.

However, the scope of application of the CMD could be confronted with today's scientific knowledge, which has expanded to encompass the concept of thresholds for carcinogens and mutagens. In such a case, where an activity would fall within the scope of the CMD, there could be a reference value based upon which a risk assessment may lead to the conclusion that there are no risks to the workers' health or safety. Consequently, based on the interpretation that is to be given to the requirement, substitution will either have to be considered or not. In light of such developments, there might still be a need for interpretation.

In practice, most Member States have used a similar wording than the CMD when requiring substitution. However, as an example, Belgium has adopted a different wording in that its implementing provisions explicitly require the results of the risk assessment to reveal a risk for workers' health or security to trigger the obligation to avoid workers' exposure by substitution.

When is substitution required as an RMM under the CAD and the CMD?

A common element that may need interpretation under both Directives to ensure coherence between the two, relates to identifying the situations in which substitution is required or whether the next RMM should be implemented based on the hierarchy provided in Articles 6.2 of the CAD and 5.2-3 of the CMD.

As previously explained, under the CAD, substitution shall be preferably undertaken except where "the nature of the activity does not permit risk to be eliminated by substitution, having regard to the activity and the risk assessment", whereas under the CMD, substitution is limited "in so far as technically possible". In view of greater consistency in the application of substitution as an RMM, it could be favourable to further elaborate over the meaning of these conditions, within the relevant provision, notably by listing elements that could be taken into account to consider that the nature of an activity does not permit the risk to be eliminated by substitution or that it is not technically possible.

It is difficult to determine how in practice an assessment that the nature of an activity permits the risk to be eliminated by substitution differs from an assessment of when substitution is technically feasible. This difference calls for interpretation, in particular since the Guidelines on the CAD do not appear to make a distinction between the two terminologies. Indeed, the Guidelines on the CAD refer to 'technical possibility' instead of the nature of the activity[49] and set the area of application of substitution under the CAD as follows: (i) where a technically viable substitute exists, and (ii) where its hazard rating is lower than that of the hazardous chemical agent used.[50] Consequently, it appears that the Guidelines to the CAD base the assessment of substitution on its technical feasibility and confirm that employers should take into account this criteria while identifying alternatives. We however have not been able to identify the legal basis within the CAD upon which these conditions apply, and in particular how they relate to article 6.2 of the CAD. The reference to the Framework Directive 89/391 in article 5.1 of the CAD could be invoked but the reference to substitution under such Directive is very general and does not refer to 'technical feasibility'. An analysis of the technical possibility of substitution seems to require to take into account the nature of the activity, but in both cases, the availability of substitutes and their capacity to offer a technical alternative would seem to be required. Neither text specifically refers to the 'economic' feasibility of the substitute, but one could argue that it is inherent to an analysis of whether the nature of an activity permits substitution, as the activity may no longer exist if the substitute is not economically viable.

We could not find a clear rationale for the above different language and believe that the terms used in both Directives could lead to various interpretations. Where the intention of the legislator is for the conditions under the CAD and the CMD to be assimilated, as could be deduced from the Guidelines on the CAD, a potential revision of the current wording to that effect would provide greater coherence between the CAD and the CMD.

The relative broadness of the conditions has led Member States to supplement it with other criteria, such as the economic viability of the possible alternative (e.g. Denmark, Germany and the UK).

[49] Guidelines on the CAD, p.22, 26-27.
[50] Guidelines on the CAD, p.27.

In comparison, under REACH, the 'substitution principle' requires a comparison of the risk profiles of different substances and may prevent authorisation of a substance of very high concern, including a CMR, when there are suitable alternative substances or technologies that are economically and technically viable (see REACH Article 55 and Recital 69). Indeed, when listed in Annex XIV of REACH, CMR 1A/1B can be authorised pursuant to Article 60.2 of REACH if the risks arising from their CMR properties are adequately controlled or failing this, under Article 60.4 if their socio-economic benefits outweigh their risks and if there are no suitable alternatives or technologies. Article 60.5 then specifies the conditions under which alternative substances and technologies shall be assessed. The 'adequate control route' is not available for substances, including CMR 1A/1B "for which it is not possible to determine a threshold in accordance with Section 6.4 of Annex I" of REACH. These articles do not discriminate between CM and R substances.

A2.2.6 Conclusions

A review and comparison of the key provisions of the CAD and the CMD, such as the provisions setting up the scope of application of these Directives, the circumstances triggering the need to consider substitutes and to apply substitution, reveals a need for greater coherence between the provisions of both Directives and potential interpretations of such provisions. The aim would be to ensure a more consistent implementation within EU Member States in view of a more systematic and easy application by employers.

Since both Directives require implementation by the Member States, they may adopt different interpretations of certain provisions where such possibility exists and this may be reflected in their legal text and/or, even when using the same legal text, in their national practices.

Additionally, the CAD and the CMD being Directives of minimum harmonization, Member States may prescribe additional requirements that go beyond those set out in the CAD and/or CMD. However, considering possible room for interpretation discussed above, an analysis of whether a given national measure goes beyond or rather below the minimum harmonization is particularly difficult. For example, whether the Directives allow Member States to allow employers to take into account economic considerations in the analysis of substitutes could be debated.

A2.3 Existing national legislation

A2.3.1 Typology of national measures in the EU

As directives of minimum harmonization, the CAD and the CMD allow Member States to adopt more stringent measures than those set out therein. Consequently, the Directives have not been implemented in the same way throughout all the Member States. While each national system has its own specificities, EU Member States have broadly selected to transpose the CAD and CMD in the following three ways:

- National measures that transpose the two Directives in two separate legal instruments
- National measures that transpose the two Directives in one legal instrument
- Implementation in a series of national measures

It must be recalled that the approach taken for such categorization remains theoretical with the limitations previously established. In that regard, certain EU Member State's legislative structures are very complex and their implementation of the CAD and the CMD may not be as clear cut in practice.

National measures that transpose the two Directives in two separate legal instruments

In many EU Member States, the CAD and CMD were transposed through two separate legal instruments. This is the case for the following 10 countries: Croatia, Denmark,[51] Greece, Latvia, Luxembourg, Poland, Romania, Slovakia, Slovenia and Spain.

In doing so, these Member States have largely replicated the texts of the two Directives, including their respective scope of application, and have thus not extended the CMD to cover reproductive toxicants. However, this does not mean that the transpositions are identical. In some cases, national legislation provides further details or relies on wording that is different from the initial provisions set out in the CAD and CMD. In other cases, some provisions have been left out of the transposing legislation. For example, several Member States have not transposed the requirements of Article 9 of the CMD pertaining to access to risk areas, such as Latvia and Poland among others.

By way of example, Spain has included the provisions of the CMD in the Royal Decree 665/1997 on the protection of workers from risks related to exposure to carcinogens at work, whereas the provisions of the CAD are transposed by Royal Decree 374/2001 on the protection of health and safety of workers from risks related to chemical agents at work. These decrees almost identically transpose the provisions of the two Directives with some additional details provided on occasion, notably with regard to the information that should be provided to workers under the CMD, and the way in which the risk assessment should be conducted under the CAD.

Transposition of the two Directives in one legal instrument

Other EU Member States have opted to implement both Directives into their existing national legislation, such as the Labour Code, Well-being at Work Code or other legislation that covers a wider range of subjects. Member States that have used this method have generally opted to extend the overall scope of the CMD to cover Reprotoxins or extended the provisions of certain CMD provisions to cover a broader range of chemicals than CMs only, therefore including reprotoxins indirectly. The report has included Belgium, France, Germany, Italy and the UK as countries following this approach.[52]

Transposition through a single instrument has been achieved in the following two ways:

A single legal instrument with separate sections implementing the CAD and the CMD

This is the case in France, which transposed the two Directives into the French Labour Code, Belgium where the Directives are transposed through the Well-being At Work Code (BCW) and Italy where such provisions are included in the Legislative Decree No.81/2008. The scope of these instruments tends to cover more than the transposition of the CAD and CMD, and other EU legislation may also be transposed therein.

[51] It should be noted that Denmark responded that they are currently merging their executive order on Chemical agents (covering reprotoxic substances) and their executive order on Carcinogens. However, the merging will affect the form and the wording of the executive order but will not affect the content or the protective level and is as such unrelated to reprotoxic issues.

[52] It must be specified that depending on the allocation of powers, there may be additional legislation complementing what the report identifies as the main legal instrument, notably in the case of federal states. As mentioned within the limitations of the analysis, such legislation is not taken into account for the purpose of providing an overview of the EU Member States implementation.

It is of note that in 2017 Belgium changed its implementation and went from having two separate Royal Decrees respectively implementing the CAD and the CMD, to integrating the provisions of both Directives into the BCW.[53] The BCW regroups existing legislation into a single, coordinated instrument with ten separate parts. Part VI of the BCW concerns chemical agents and CMRs. It is sub-divided into separate titles, the first of which is applicable to all chemical agents and transposes the provisions of the CAD. The second title is dedicated to CMRs and transposes the provisions of the CMD.

A single legal instrument with a unique system for all chemicals within the scope of the CAD and CMD

In the UK and Germany, a single national legal instrument is used to implement both the CAD and the CMD. However, the legislation sets up a unique system which appears to combine the requirements of the CAD and the CMD. These systems are difficult to analyse from a CAD and CMD transposition perspective because certain measures from the CMD, limited to carcinogens and mutagens under EU legislation, are extended to other chemical agents, while other specific measures may still apply to CM (UK) or CMR (DE) substances only.

Germany has combined the requirements of the CAD and the CMD into the 2010 Hazardous Substance Ordinance, which is generally applicable to 'hazardous substances' for which it provides an extensive definition. However, the Ordinance is divided into sections which do not have the same scope. All substances which fall under the scope of the Ordinance are subject to a multi-tiered risk management system under which employers must first carry out a risk assessment. Employers must preferably substitute hazardous substances and where the risk assessment identifies occupational exposure to such substances, employers must comply with basic obligations and apply general protection measures.[54] If these measures are not sufficient to rule out the risk of oral, dermal or inhalation exposure, supplementary protective measures must be taken.[55] The 2010 Hazardous Substance Ordinance has extended certain CMD provisions too all substances for which the risk assessment has revealed a risk, therefore including reprotoxins. This is notably the case regarding substitution, which is a general requirement. However, there are also certain CMD provisions which have either deliberately been extended to reprotoxins (e.g. demarcation or the assessment of exposure by measurements), or deliberately not been extended to reprotoxins (e.g. record keeping for 40 years or health surveillance).[56] The 2010 Hazardous Substance Ordinance also provides for exemptions,[57] and is supplemented by technical rules on hazardous substances which may be followed on a voluntary basis, the compliance of which creates the assumption that the employer conforms with the Ordinance.

The United Kingdom (UK) has set out its requirements in the 2002 Control of Substances Hazardous to Health Regulations (COSHH), which although it globally implements the requirements of the CAD and CMD, has a broader scope and particular system. It covers all substances which qualify as being 'hazardous to health' according to the definition provided therein. COSHH requires the performance of a risk assessment where the work carried out could expose employees to any substance hazardous to health, which includes the consideration of elements both from the CAD and the CMD. There is a general obligation to prevent employee exposure to such substances, but where this is not reasonably

[53] The CAD was transposed through Royal Decree of 11 March 2002 on the protection of workers' health and safety against risks related to chemical agents at work. The CMD was transposed in the Royal Decree of 2 December 1993 regarding the protection of workers against risks related to exposure to carcinogens and mutagens at work.

[54] Milieu/RPA Report, 2012, p.132; Art. 6-8 of the 2010 Hazardous Substance Ordinance.

[55] Milieu/RPA Report, 2012, p.132; Art. 9 of the 2010 Hazardous Substance Ordinance.

[56] Milieu/RPA Report, 2012, p.132; Art. 10 of the 2010 Hazardous Substance Ordinance.

[57] *Ibid.*

possible, COSHH imposes a duty of control through the adoption of appropriate protection measures.[58] Where the exposure involves CMs or biological agents, additional measures are required. The legislation also allows for exemptions regarding certain requirements but this possibility is not specific to reprotoxins and has rarely been used.

Implementation in a series of national measures

In several EU Member States, the CAD and the CMD have been transposed into a number of national measures which may be a part of legal instruments covering the implementation of other Directives as well. In that respect, certain EU Member States have an overarching act on occupational health and safety that gives the authority to implement provisions set out in more specific legislation, creating a pyramidal structure, where several acts may contain obligations for employers. In such a case, the provisions of the two Directives are scattered across several measures, generating a complicated situation to analyze from an implementation stand-point. Among the countries following this typology, there does not appear to be a particular trend to include reproductive toxicants with carcinogens or mutagens.

Countries that follow this typology include, e.g. Austria, Bulgaria, Cyprus, Czech Republic, Estonia, Finland, Hungary, Ireland, Lithuania, Malta, the Netherlands, Sweden and Portugal. By way of example:

Malta may serve as an illustration of a pyramidal structure that comprises a number of tiers. The main statute based upon which other legal acts were adopted is the Occupational Health and Safety Authority Act. This measure allows the responsible Minister to adopt subsidiary legislation (S.L.) to regulate, monitor and enforce health and safety requirements at the workplace and the prevention of risks related thereto.[59] Accordingly, Malta has adopted two pieces of subsidiary legislation to implement the legal requirements of the CAD and CMD, respectively S.L. 424.24 (LN 227/2003) on the Protection of the Health and Safety of Workers from risks related to Chemical Agents at Work Regulations, and S.L. 424.22 (LN 122/2003) on the Protection of the Health and Safety of Workers from risks related to Carcinogens and Mutagens at Work Regulations. Within Section 7 of S.L. 424.24 on the arrangements to deal with accidents, incidents and emergencies, reference is made to additional specific regulations for the first-aid, fire-fighting, evacuation, warning and communication measures that must be taken. These are set out in S.L. 424.13 on Work Place (First Aid) Regulations, S.L. 424.15 on Work Place (Minimum Health and Safety Requirements) Regulations and S.L. 424.16 on Work Place (Provision of Health and, or Safety Signs) Regulations.[60]

The Netherlands has transposed the two Directives through three acts which together form the Working Conditions Legal Instruments: Working Conditions Law of 18 March 1999, Working Conditions Decree of 15 January 1997 regarding the safety, health and wellness in the workplace and the Working Conditions Regulation of 12 March 1997 implementing provisions of the Working Conditions Decree. All three acts implement the CAD, while the CMD is implemented through the Decree and Law. Provisions implementing the legal requirements of both Directives may therefore be found in the same measures.

The Czech Republic has also transposed the Directives in several pieces of legislation, which range from general requirements, found in superior legislation, to specificities, which are provided in lower legislation. First, the general requirements on occupational health protection law are given in the

[58] Regulations 5-13 COSHH.

[59] Milieu/RPA Report, 2012, p.248.

[60] Where these reference measures do not implement the CAD legal requirements, Malta could potentially fall under the approach set out in section 2.2 a).

Labor Code (Law 262/2006) and the Public Health Law (Law 258/2000). Next, the legal act which transposes the CAD and the CMD is Law 309/2006. However, the detailed requirements of both Directives are found in Government Decree 361/2007, determining the conditions for the protection of health at work. Moreover, these measures are completed by the Government Decree 432/2003, laying down conditions for job categories, limit values of biological exposure tests, sampling conditions of biological material for biological exposure tests and requirements for reporting work with asbestos and biological agents.[61] Additionally, the Czech Republic has a law on chemical substances and preparations which sets out the procedures for determining which substances are reprotoxic, i.e. Law 365/2003.[62]

A2.3.2 Future developments at the national level

The questionnaires asked EU Member States whether they are contemplating or in the process of changing their national transposition legislation. Almost all Member States have replied that they have no plans to change their national regulation of reprotoxic substances.

Sweden has submitted a proposal to amend the Chemical Hazards in the Working Environment (AFS 2011:19) which should notably introduce clarifications on what is meant by chemical products and chemical hazards, modifications to markings and the introduction of OELs instead of permits for a number of substances. Additionally, the Provisions on Hygienic Exposure Limits (AFS 2015:7) was replaced as of 21 August 2018 by AFS 2018:1, which will amend Swedish OELs for reprotoxic substances.

While France's legislation is not under revision, the French Agency for Food, Environmental and Occupational Health & Safety, responsible for the development of OELs, has proposed atmospheric limit values for six substances since 2017. The Agency has also recommended BLVs and BRVs to improve the monitoring of exposure in workers to several substances.

Ireland has also proposed additions or changes to the OELV in the 2016 Code of Practice for the Chemicals Agents Regulations, which may concern reproductive toxins.

Denmark responded that they are currently merging their executive order on Chemical agents (covering reprotoxic substances) and their executive order on Carcinogens. However, the merging will affect the form and the wording of the executive order but will not affect the content or the protective level and is as such unrelated to reprotoxic issues.

Germany responded that their new "Mutterschutzgesetz"[63] recently entered into force on 1st January 2018 and it contains several measures concerning pregnant women. It also includes specific safety measures for possible contact with reproductive toxic substances.

It must also be noted that Member States are gradually implementing Directives 2017/164/EU, which notably establishes a fourth list of indicative OELs, and Directive 2017/2398/EU, which amends the CMD. Luxembourg for example deposed a bill for the Regulation transposing Directives 2017/164/EU in March 2017, which was still in legislative procedure as of 27 March 2018. Spain intends to implement Directive 2017/2398/EU by 17 January 2020 and is also in the process of changing certain OELs in 2019.

[61] Amended by Decree 107/2013.
[62] Milieu/RPA Report, 2012, p.61.
[63] Mutterschutzgesetz available at: https://www.gesetze-im-internet.de/muschg_2018/MuSchG.pdf.

A2.3.3 Third country measures and approaches

Non-EU EEA countries and Switzerland

Among third countries, it is the non-EU EEA (and EFTA) countries which have the closest system to the EU's. Since the CAD and CMD were incorporated into the EEA Agreement, these three countries have transposed the two Directives into their national legislation, while including their national specificities. The same applies to Switzerland. The EEA countries and Switzerland do not follow a common typology. Where Iceland has transposed the two Directives through two separate regulations, respectively transposing the CAD and the CMD, Norway has transposed the two Directives into two measures with broader scopes and Switzerland has incorporated the Directives in a broad single instrument, which forms its primary legislation regarding the country's chemical regime. Liechtenstein has used a more particular method by cross-referring the CAD and the CMD in national legislation and declaring them directly applicable, as *lex specialis*, in Liechtenstein.

Iceland and Norway have also extended at least part of the scope of their national measures dealing with carcinogens and mutagens to include reprotoxic substances, although Norway also has specific provisions for carcinogens and mutagens only.

Non-EEA/EFTA third countries

Legal frameworks

With the exceptions of India and the State of California, none of the other non-EEA countries appear to have adopted specific legal acts for occupational exposure to CMR substances. These substances fall under broader measures which may deal with chemicals or workplace safety and health in general.

Table A2-2: CMR legislation in non-European countries

Country	CMRs treated same as other chemicals	R treated differently
Australia	Yes	No
Brazil	Yes	No
Canada	Yes	No
China	Yes	Questionable
India	Yes, with exception	Selected employment of women only
Japan	Yes	No
USA	Yes, except California (see below)	California only

By way of example, Brazil has a series of standards to deal with occupational health, environmental risk prevention programs, occupational health examination programs and safety signs. No measures appear to be specific to chemical agents or CMRs at the workplace.

To the contrary, in India, while there is no specific regulatory information for CMRs, there is a regulation to protect female workers from occupational exposures to "reprotoxic substances" in the context of workplace safety. This approach applies specifically to the "female workers." Under *The Factories Act, 1947*, employment of women in hazardous processes which might cause a potential effect on their reproductive health is restricted.

Substantive requirements

Generally speaking, there appears to be a greater focus on carcinogens than on mutagens or reprotoxins in a number of the third countries, including Brazil, South Korea and the USA. Another common feature is that none of the non-EEA/EFTA third countries seem to have a system in place that requires the substitution of C, M and/or R as the main risk management measure to be taken when dealing with such chemical agents. Their main provisions to regulate such substances appear to be through the establishment of OELs and the communication of hazard information through labelling and classification requirements, mostly following those of the GHS.

Contextualising third country measures

The sectors in which the local industry is active can explain why certainly measures have been implemented or not in some of the third countries. For example:

Norway has adapted its legislation to accommodate the specificities of its dominant fishing and petroleum industries. It has regulations pertaining to petroleum activities, in which a particular paragraph deals with the chemical health hazards related to such activities, and Regulations concerning the working environment, health and safety of workers on board ships.

Additionally, countries may also decide to adopt more specific measures following major events and media coverage. This was also the case for Norway where CMRs became a relevant topic in 2007-2008 after a series of accidents led to workers' exposure to carcinogenic and reprotoxic substances and a lot of media attention was brought upon the cases.

Example of an 'advanced' approach: California's Prop. 65

Within the last year, the USA has seen a remarkable surge in interest in developmental effects from chemicals, as the US state California has fully implemented its newest regulation under the *Safe Drinking Water and Toxic Enforcement Act of 1986*, better known as Prop 65. Although officially and legally the extent of the legislation is confined to the State of California, it has affected all interstate commerce within the USA due to its stringent labelling requirement on anything sold or available through internet commerce to residents of the State of California. The details of the rather stringent labelling requirements themselves are beyond the scope of this document especially since these are primarily aimed at consumers rather than occupational uses, although those are included as well. The labelling is required to state that "This product can expose you to chemicals including Chemical X which is/are known to the State of California to cause cancer/ birth defects or other reproductive harm" (with various modifications). The labelling regulation which went into full effect on 30 October 2018, gained massive attention especially given the breadth of chemicals it includes (Prop 65 is based on a list of well over 300 substances considered to be reprotoxins). Additional confusion is caused by the so-called Safe Harbor provisions which provides *de minimis* exposure levels for some chemicals, below which such warnings are not required.

There are four aspects which are totally different from regulations elsewhere:

1. The presence of *de minimis* or Safe Harbor total exposure limits for selected chemicals, above which a warning is required;
2. The absence of the word mutagenic in the regulation although the presence of M1 classification may be inferred from the "birth defects" language;
3. The applicability of the regulation to both direct and indirect, environmental human exposures;
4. The inclusion of drugs in a consumer-aimed regulation.

Safe Harbor limits are (generally) based on total exposure not exposure limit concentrations contrary to most exposure limits presently in place (one might argue that Biological Limit Values are measures of total exposure). The concept of *de minimis* limits in the regulation of carcinogenic or developmental effects is also quite rare.

Contrary to most of the world, including the EU where carcinogenic and mutagenic (and rarely reproductive effects) are regulated as similar/one entity(s), here carcinogenic, birth defects and developmental effects are all included. One can argue that inclusion of birth defects might be considered equivalent to an M1(A) GHS/REACH classification.

A regulatory approach that mixes environmental human (secondary to releases into the environment) and direct (consumer) human exposures is also quite rare. Here the Safe Harbor levels may also apply to environmental exposures but this has been considered murky.

All together Prop 65 by default has driven the adoption and analysis of developmental effect labelling for nearly all US products/articles, without it being a federal, nation-wide law with associated regulations.

A2.4 Synthesis of findings

A2.4.1 Regulation of reprotoxic substances

Eight EU Member States have taken advantage of the fact that the CAD and CMD are 'minimum harmonization' directives and have either extended the overall scope of their national legislation transposing the CMD to cover reprotoxins, or extended certain provisions of the CMD to either reprotoxins or a broader range of chemical agents than just carcinogens and mutagens and therefore covering reprotoxins. This is the case in Austria, Belgium, Czech Republic, Finland, France, Germany, Sweden and the United Kingdom. Where such initiatives have not been taken, reprotoxins remain under the scope of the national legislation that has transposed the CAD.

As a result, there is a large variation as to the legal requirements that apply to reproductive substances across EU Member States. Three approaches may be distinguished among the EU Member States regarding the legal requirements they impose on reprotoxic substances:

- EU Member States that have not extended the CMD provisions to reprotoxins;
- EU Member States that have explicitly extended CMD provisions to reprotoxins; and
- Other approaches.

Table A2-3: Summary of national legislation in the EU-28							
Member State	A: CAD & CMD in 1/2/more than 2 pieces of legislation?	B: Same rules for CMs and Rs?	C: Substitution of Rs whenever workers exposed or likely to be exposed?	D: Closed system explicitly required as second RMM for Rs?	E: Exposure minimisation requirement for Rs?	F: CAD 11 R IOELVs binding?	G: Record keeping for >40 years for Rs?
Austria	>2	Yes	Yes	Yes	Yes	Yes	Yes
Belgium	1	Yes	Yes	Yes	Yes	Yes	Yes
Bulgaria	>2	No	No	No	No	Yes	Yes[64]
Croatia	2	No	No	No	No	Yes	No
Cyprus	>2	No	No	No	No	Yes	No
Czech Republic	>2	Yes	Yes	Yes	Yes	Yes	Yes
Denmark	2[65]	No	No	No	Yes	Yes	No
Estonia	>2	No	No	No	No	Yes	No
Finland	>2	Some (only C)	Yes	No	No	No	No
France	1	Yes	Yes	Yes	Yes	No	Yes[66]
Germany	1	Some	Yes	Yes	Yes (exempt if below OEL)	Yes	No
Greece	2	No	No	No	No	Yes	No
Hungary	>2	No	No	No	No	Yes	No[67]
Ireland	>2	No	No	No	No	Yes	No
Italy	1	No	No	No	No	No	No
Latvia	2	No	No	No	No	Yes	No
Lithuania	>2	No	No	No	No	No	No
Luxembourg	2	No	No	No	No	Yes	No
Malta	>2	No	No	No	No	Yes	No
Netherlands	>2	No	No	No	No	Yes	No
Poland	2	No	No	No	No	Yes	No
Portugal	>2	No	No	No	No	No	No
Romania	2	No	No	No	No	No	No
Slovakia	2	No	No	No	No	Yes	No
Slovenia	2	No	No	No	No	Yes	No
Spain	2	No	No	No	No	Yes	No
Sweden	>2	Yes	Yes	Yes	Yes	Yes	No
United Kingdom	1	Some	Where exposure	No	No	Yes	Yes
Total % of Member States[2] (Yes)	***1: 18% 2: 36% >2: 46%***	***18% (or 29% if also 'some')***	***25%***	***21%***	***25%***	***78%***	***21%***
Total % of workforce[2] (Yes)	***1: 55% 2: 25% >2: 19%***	***19% (or 52% if also 'some')***	***52%***	***38%***	***39%***	***71%***	***32%***
Notes: 1: Germany: 'slight' level of risk available for Rs. Orange cells - presumed/inferred 2: Sums of percentages may not amount to 100% due to rounding. Sources: Annex 3, Milieu/RPA 2012, COWI reports, Consultation Round 1, Consultation Round 2							

[64] Health records: 50 years (Ordinance No. 3 of 25 January 2008 on conditions and order for implementation of activities of occupational medicine services).

[65] Denmark responded that they are currently merging their executive order on Chemical agents (covering reprotoxic substances) and their executive order on Carcinogens.

[66] Medical records: 50 years (R4624-22 to 28).

[67] But 50 years for carcinogens.

A2.4.2 EU Member States that have not extended the CMD provisions to reprotoxins

The majority of EU Member States have not adopted more stringent obligations for reprotoxic substances than those set out in the CAD. Therefore, in these Member States, reprotoxic substances remain covered under the national legislation transposing the obligations of the CAD and are only subject to the legal requirements set out therein.

The countries that have opted for this approach mainly correspond to those that have also chosen to transpose the CAD and the CMD through two separate legal instruments. This is the case in Poland, Denmark, Romania and Spain. These countries also tend to maintain the delineation between the scopes of the two Directives: the legal instrument transposing the CAD is generally applicable to hazardous substances, whilst the national measure implementing the CMD is restricted to CMs.

For example, Romania has two main acts transposing the CAD and CMD: Governmental Decision No.1218/2006 and No.1093/2006, respectively. These acts transpose the requirements of each Directive with very few alterations. The scope of Governmental Decision No.1093/2006 reproduces the legal requirements of the CMD and its scope of application, which is limited to CMs. Consequently, reprotoxins remain covered under the national provisions transposing the CAD requirements, i.e. Governmental Decisions No.1218/2006 and the corresponding legal requirements.

In addition, some EU Member States that have transposed the CAD and CMD in one or more than two legal instruments have also chosen not to extend the scope of the CMD to reprotoxic substances. This is the case in Italy, which implements the two Directives through a single measure, and Hungary, which relies on a number of legal instruments.

Italy has a single piece of legislation which transposes both the CAD and the CMD, Legislative Decree No.81/2008. The instrument has separate titles for the provisions which transpose the legal requirements of each Directive, and title IX, which covers hazardous substances, is sub-divided into separate sections for chemical agents and CM substances. As the latter section is not extended to cover reprotoxins, such substances remain under the scope of the sub-title dedicated to all chemical agents. The way the different chemical agents are regulated in the legislative decree therefore largely reproduces the scopes of the CAD and CMD.

A2.4.3 EU Member States who have explicitly extended some or all CMD provisions to reprotoxins

As mentioned above, some EU Member States have extended the scope of their national legislation transposing the CMD to cover reprotoxic substances, subjecting them to the more stringent rules set out in the CMD. This approach is often characterised by the inclusion of a specific reference to reprotoxic substances in the national legislation transposing the CMD. To define reprotoxins, Member States either refer to the CLP classification or provide specific definitions. Those that have incorporated an explicit reference to reproductive toxins when transposing the provisions of the CMD into their national legislation, notably include Austria, Belgium, Czech Republic and France.

Belgium and France have similar systems whereby a single instrument is used for the transposition of both the CAD and CMD but separate sections are provided to deal with chemical agents and CMRs. In both countries, reprotoxins have been added into the scope of the provisions transposing the legal requirements of the CMD. Accordingly, the relevant sections no longer refer to CMs but to CMRs. Both

countries define reprotoxins as a substance or mixture that meets the criteria of classification as Category 1A/1B of reprotoxic substance, as set out in Annex I of the CLP.[68]

France also allows the Ministers of Work and Agriculture to provide an additional definition in a joint act. According to the information upon which this report is based, no such act has been adopted.

However, not all EU Member States include reprotoxins by referring to the CLP. As an example, the Czech Republic has implemented the requirements of the CAD and CMD through several instruments which do not all have the same scope. Nevertheless, the main measure implementing the specific requirements of both the CAD and the CMD is Government Decree 361/2007, which applies to reprotoxins of Categories 1 and 2 as defined in the Law on Chemical Substances and Preparations 365/2003. This law states that reprotoxic substance are substances or preparations which when inhaled, digested or absorbed through the skin may cause or exacerbate non-hereditary adverse impacts on the offspring or harm male or female reproductive capability. Article 5 further elaborates over the definition of such substances and states that this is determined by means of a calculation set out in another implementing regulation.[69]

A2.4.4 Other approaches

Germany and the UK have singular approaches which have been detailed in section A2.3.1 and seem to combine the legal requirements of the CAD and the CMD. Both countries have implemented the CAD and the CMD through a single measure that has a broad scope and covers 'hazardous substances' in Germany, or 'substances hazardous to health' in the UK.

Moreover, Germany has a set of specific provisions that are applicable to CMRs while the UK has a set of provisions applicable only to CMs. However, these specific requirements are not applicable under the same circumstances as laid out under in the CMD, owing to the specificity of each country's system.

As a brief summary, Germany has combined the requirements of the CAD and the CMD into the 2010 Hazardous Substance Ordinance which is applicable to 'Hazardous Substances'. All covered substances are subject to a specific multi-tiered risk management system that gives rise to obligations where a risk is identified and includes potential exceptions. However, where a CMR substance is involved, additional special protective measures must be implemented. Through this specific system, Germany appears to combine the requirements of the CAD and CMD although certain CMD provisions have either deliberately been extended to cover reprotoxins, or deliberately exclude reprotoxins.

The United Kingdom has set out its requirements in the 2002 Control of Substances Hazardous to Health Regulations (COSHH), covering all substances that qualify as being 'hazardous to health' according to the definition provided therein. COSHH requires the performance of a risk assessment where the work carried out could exposure employees to any substance hazardous to health, which includes the consideration of elements both from the CAD and the CMD. There is a general obligation to prevent employee exposure to such substances, but where this is not reasonably possible, COSHH imposes a duty of control that entails the adoption of appropriate protection measures.[70] Where the exposure involved CMs or biological agents, additional measures are required.

Additionally, Finland has a unique approach since it is the only country which appears to have a separate instrument to deal with reprotoxins. Indeed, Finland adopted the Governmental Decree on

[68] Art. VI.2.2, §3 Belgian Code of Well-being; R.2212-60 French Labor Code.
[69] Milieu/RPA Report 2012, p.62.
[70] Regulations 5-13 COSHH.

Agents Causing Risk to Reproductive Health in Work and the Prevention of Such Risk (603/2015), which lays down provisions on chemical, biological and physical agents causing risk to reproductive health in work. The Decree notably covers reprotoxins of Cat. 2 and calls for the replacement of agents that are hazardous to reproductive health when technically feasible and reasonably practical. The other obligations amount to a combination of those of the CAD and the CMD. However, all the requirements set out in the Decree are also applicable to carcinogens and mutagens but specific requirements limited to carcinogens and mutagens exists as well.

A3 The Threshold vs. Non-threshold Paradigm

A3.1 Introduction

One of the issues considered in this report is whether the current paradigm of threshold (T)[71] acting substances addressed by CAD and non-threshold (NT) acting substances addressed by CMD is still relevant, efficient and effective at controlling risks to workers' health.[72] This includes the issue whether (as a default approach, i.e. unless proven otherwise) reproductive effects should (or should not) be treated as having a threshold. As an add-on to the core analysis, the need for the extension of the non-threshold approach to other types of chemical hazards (sensitisers) is briefly considered.

Key findings

The threshold vs non-threshold paradigm is one of the reasons for providing additional protection in the CMD and the differentiation between threshold and non-threshold effects is still relevant, effective and efficient, although developments in scientific knowledge show that some carcinogens are now assumed to act through a threshold mode of action.

On the basis of a review of scientific literature, this report argues that the threshold approach continues the adequate default approach for reproductive effects, although there may be a small number of substances for which a non-threshold approach is more appropriate, meaning that a determination of the most appropriate approach should take into account the specificities of each substance. This conclusion takes into account the fact that a small number of reprotoxic substances can act through an endocrine disrupting mode of action. For EDCs currently a debate is ongoing about the most suitable paradigm for risk characterisation.

As an add-on to the core analysis, the need for the extension of the non-threshold approach to other types of chemical hazards is briefly considered on the example of sensitisers. The majority opinion of the experts and authorities appears to be that, for skin sensitisers, thresholds for induction for sensitisation exist and health-based reference values based on the threshold assumption can likely be determined (despite some methodological difficulties). For respiratory sensitisers, thresholds for adverse effects (induction of sensitisation) exist but are difficult to determine with currently available models and methods, suggesting that the non-threshold approach may thus be a more practical approach to controlling risks from occupational exposure.

Approach

The conclusions in this section are based on a literature review and any information collected through consultation for this study. A qualitative review has been carried out which aimed to identify the prevailing scientific opinion. Conclusions on the relevance, effectiveness and efficiency of additional protection for non-threshold risks provided by the CMD are based on a qualitative evaluation carried out by the study team.

Limitations/uncertainties

[71] The term 'threshold' means a dose or concentration, below which adverse effects of a substance are not expected to occur, i.e. are undistinguishable from background rates.

[72] It should be noted that this is only one of several distinctions between the CAD and CMD, one of the other ones being the severe health consequences that carcinogens can have.

The conclusions in this study are based on what has been identified to be the prevailing scientific opinion. However, it needs to be recognised that there is always a diversity of scientific opinions and there may be a minority scientific opinion that is not in agreement with the findings in this study. In particular, there is a range of opinions regarding whether thresholds exist for adverse effects that occur via the endocrine disruption mode of action.

The analysis in this section always focuses on a specific effect, i.e. reproductive ill health or sensitisation. However, many substances have multiple hazard classifications and, although the threshold approach may be appropriate for one effect, it may not necessarily be appropriate for another effect.

Although the threshold approach may sometimes be adequate in theory, the value of the threshold may in some instances be difficult (or impossible) to determine or may be close to (or below) background exposure levels, suggesting that the non-threshold approach may be more appropriate.

A more detailed review of the scientific literature and the legislative approaches is provided in Annex 3. A detailed review of the applicability of the different threshold/non-threshold approaches to skin and respiratory sensitisers is provided in Annex 4.

A3.2 Evaluation of the threshold vs. non-threshold paradigm

This section argues that then threshold versus non-threshold paradigm (i.e. establishing additional requirements for non-threshold substances) is still a relevant, effective and efficient approach, although it is recognised that a substance-by-substance approach may in some instances be more appropriate than a 'block' approach to a group of substances belonging to a specific hazard class.

A3.3 Relevance

The key questions with regard to relevance are:

- **New knowledge:** Is there new scientific knowledge (or opinion) suggesting that the dual approach is no longer relevant?
- **Current needs and problems:** Is a threshold vs non-threshold approach still appropriate to ensuring worker protection and a level playing field in the internal market?
- **Adaptability:** Is the dual approach adaptable to future technological or scientific advances?

The distinction between threshold and non-threshold approaches continues to be relevant in terms of the current scientific thinking. However, scientific knowledge now distinguishes between carcinogens acting via a threshold effect and those believed to act via a non-threshold mechanism, suggesting that a substance-by-substance approach may be more relevant than a risk class approach.

Most respondents[73] to the consultation agreed that the distinction between threshold and non-threshold substances is still relevant and necessary, although there was less agreement from trade union representatives and some dissension within the set of Member State Authorities. In particular it is argued that, based on the current state of knowledge, reprotoxic substances are threshold substances and that it is therefore possible to set health-based limits.

[73] Including occupational health and safety practitioners, industry (associations and individual company respondents) and Member State authorities, but not trade unions.

It is clear that the broad needs remain the same, i.e. there is a need to protect workers' health and to prevent employers (and Member States) undercutting one another by means of a race to the bottom through a lowering of worker protection standards. However, in light of the changing views on thresholds and carcinogens, it could be argued that the legislative needs with respect to the combined objectives of worker protection and ensuring a level playing field have changed – the requirements of the CMD do not appropriately reflect the level of risk management needed to address the risks posed to workers from occupational exposures where thresholds for effects exist.

The current framework is not easily adaptable to future technological and scientific developments. As noted above, it is currently out of date with respect to the latest scientific thinking on the threshold/non-threshold paradigm for carcinogens. In part, this is likely to be due to the fact that the legal form of the legislation is directives rather than regulations, which would be more easily adapted over time. It may also reflect the fact that there may be significant objections to a lowering of protection for workers against exposures to carcinogenic substances, even though a threshold for effects may be considered to exist.

Science keeps evolving and new studies emerge all the time. It is therefore possible that additional studies will lead to the conclusion that some carcinogens currently believed to be non-threshold do have a threshold or that some carcinogens that are currently expected to have a threshold have a lower threshold. This argues for greater flexibility within the CMD, for example, to have two approaches to risk management – one for threshold and one for non-threshold substances. Several respondents argue that the distinction between threshold and non-threshold approaches should also apply to individual carcinogens, and that regulation of these should be differentiated according to the actual risks posed by these substances and, hence, also taking into account the possibility to define a threshold or not. In other words, the potential should exist in the legislation for carcinogens to also be regulated under a health-based approach where thresholds for effects are considered to exist.

A3.3.1 Effectiveness

The key question with regard to effectiveness is:

- Is there a practical difference between the approaches in the CAD and CMD?
- How effective is the T vs NT approach in terms of protecting workers and ensuring a level playing field in the internal market?

The differences between the CAD and CMD in terms of their practical implementation are analysed elsewhere in this report. Both approaches are effective in terms of reducing or eliminating the risks from the respective substances within their scope. The more stringent requirements of the CMD stem from both the prevailing scientific view at the time of its adoption that postulated that carcinogens do not have a threshold and the severe health effects of carcinogenic and mutagenic substances.

A3.3.2 Efficiency

The key questions with regard to efficiency relate to the cost-effectiveness of the legislative framework and the overall balance between net costs and net benefits. The key questions are:

- Does the dual approach reduce costs for companies and authorities, or does it lead to unnecessary costs?
- To what extent are the costs proportionate to the benefits it has generated?

The reliance on thresholds where these exist helps ensure that employers do not incur unnecessary costs from the risk reduction perspective, since it enables minimisation to levels where there should be no residual risks.

Given that the CMD does not recognise the existence of thresholds for effect, it may be leading to an unnecessary burden for employers where measures other than substitution or closed systems could be adopted to meet the exposure thresholds. This is somewhat mitigated by the more extensive use of Binding OELVs, which are now being implemented for a large number of substances. Whilst the setting of these does not absolve employers legally from their responsibility to prevent or minimise exposure, they do provide a quantitative level of ambition for employers.

A3.4 Reprotoxic substances

Reprotoxic substances have always been considered to be threshold substances and this continues to be the case (although there is debate as to the existence of a threshold for some reprotoxins having an endocrine mode of action).

In Annex 4, we provide a 'current state of science' opinion on the threshold- vs. non-threshold of action for reproductive toxicants. Because, however, this opinion has been fed from the respective EDC-discussion and because reprotoxic substances often are EDC, the respective "state of science" opinion on EDC has been included in our analysis.

Specifically, we address the following topics:

- Defining and quantifying thresholds;
- Mechanistic background of threshold vs. a non-threshold mode of action for adverse health effects;
- "State of science" evidence of thresholds and (non-)monotonic dose responses for EDC;
- "State of science" evidence for thresholds and threshold quantification on reproductive toxicants (EDC or non-EDC type of substances); and
- Discussion and conclusion.

There has been a lot of discussion regarding reprotoxins acting as EDCs. The evidence is limited and only available for very few compounds. A good comparison of in vitro dose levels and in vivo exposures has not been made nor has a comparison of in vitro effects and in vivo adverse effects. It is quite possible that some reprotoxins may be EDC with diagnosed adverse in vivo health effects but such links appear very tenuous at present. We have included a detailed analysis of the EDC vs reprotoxins debate in Annex 4, but acknowledge that this matter has not been yet resolved. The recent Communication from the Commission (COM(2018)/734)[74] acknowledges that knowledge gaps still exist for EDCs, including whether the 'safe threshold' principle, i.e. the dose below which no adverse effect is expected to occur is applicable to endocrine disruptors, with "a share of scientists" being of "the view that a safe threshold cannot be established". Although this Communication can be expected to have an indirect impact on some reprotoxic substances in the future, it is too early to be able to reliably assess this impact.

Based on recent state of the science reports, national or international committee statements and workshop conclusions on reproductive toxicity and endocrine disruption, there is some uncertainty and hence questions over as to whether the existing threshold paradigm should generally be maintained. However, the uncertainties do not currently lead to a change in the existing default

[74] See http://ec.europa.eu/transparency/regdoc/rep/1/2018/EN/COM-2018-734-F1-EN-MAIN-PART-1.PDF

assumption of the existence of a threshold for reproductive toxicants in general. There may be exceptions, though, where non-default, case-by-case evidence leads to a non-threshold conclusion for individual reproductive toxicants.

Overall, despite there being no official conclusion which can be cited, we find it coherent with this "state of the science" to conclude that a non-threshold assumption will not reflect the typical case and a threshold approach still provides an adequate default assumption for EDC. However, there may be (probably rare) exceptions to this overall threshold-assumption, which could be assessed on a case-by-case basis. For most of the chemicals discussed in detail in this document, with the possible exception of BPA, an EDC effect leading to reproductive toxicity has not been established.

On the other hand, from an OSH perspective, there are potential arguments for treating some reprotoxic substances as non-threshold substances, for example where the threshold cannot be reliably quantified or where it is below or close to background exposure levels.

In terms of this study, another concern has been the appropriateness of the type of animal studies conducted for assessment purposes. Many ways have been designed to evaluate male and female reproductive toxicity. In developing DRRs for the 30 substances (see Annexes 10-21 and Annex 1), the following assumptions have been made:

- Female and male reproduction are adequately assessed in the studies we selected (this becomes problematic when the number of studies becomes extremely limited);
- Although it would have been nice to distinguish between short and long-term studies, we always selected the lowest threshold, most likely from the longest term/generation study;
- Short term effects/exposures generally have higher thresholds;
- Extended exposure studies show higher sensitivity i.e. lower thresholds; and
- Extended generation studies whether multiple generations or extended follow up, always appear to have the highest sensitivity i.e. the lowest thresholds.

Thus, the selection of the lowest threshold a priori favours the long-term multigeneration studies when they are available.

A3.5 Other categories of chemicals

In terms of appropriateness of the NT approach to chemicals (other than CMR), this report focuses on skin and respiratory sensitisers. A detailed discussion is provided in Annex 5 and the conclusions are summarised below.

A3.5.1 Sensitisers

The consensus of the competent experts and authorities seems to be that thresholds for induction do exist:

- **Skin sensitisers:** thresholds for adverse effects (induction of sensitisation) exist and health-based reference values based on the threshold assumption can likely be determined (despite some methodological difficulties)
- **Respiratory sensitisers:** thresholds for adverse effects (induction of sensitisation) exist, but – with currently available models and methods - are difficult to determine

However as noted, the experimental methods in use including in silico models are not advanced enough to determine accurate thresholds (for use in standard setting[75]) at this time especially in view of the highly variable sensitive populations that exist within the workforce. PPE on the other hand has proven very effective in preventing especially skin sensitisation.

Quantifying human skin exposure to sensitisers is difficult to achieve under workplace conditions, so human dose–response relationships would be difficult to establish. Dose-response information can be obtained from adequately in vivo testing. However, for reasons of animal welfare skin sensitisation testing is mainly performed nowadays using in vitro assays, suitable for classification, but with limited possibilities to inform about dose-response under realistic exposure conditions. For respiratory sensitisers derivation of a health-based OEL will most likely depend on the amount of quantitative human data from workplace experience and it might be possible or not on a case-by-case basis.

The majority opinion of the experts and authorities seems to be that thresholds for induction for sensitisation do exist, health-based reference values based on the threshold assumption can likely be determined (despite some methodological difficulties) for skin sensitisers only. For respiratory sensitisers, thresholds for adverse effects (induction of sensitisation) exist, but – with currently available models and methods - are difficult to determine, and a non-threshold approach may thus be a more practical approach to controlling risks from occupational exposure. However, PPE on the other hand has proven very effective in preventing especially skin sensitization.

A3.6 Synthesis of findings

The threshold vs non-threshold paradigm continues to be relevant, effective and efficient, although developments in scientific knowledge suggest that a substance-specific focus may be preferable to a uniform approach to all substances belonging to a specific hazard class.

With regard to whether reprotoxins have safe levels of exposure i.e. thresholds, there are a few schools of thought as to whether this is the case but the majority scientific opinion is that the appropriate default position is that there are thresholds, even though they may be difficult to quantify. This section focuses on reproductive and developmental toxicity outcomes outside the Endocrine Disrupting Chemicals (EDC) realm. There are very few chemicals which are thought to exert reproductive effects via EDC/hormone like action (although this conclusion may change as additional studies become available) and the majority of reprotoxins appear to have different mechanisms of action under the current (majority) thinking. However, Annex 4 offers a detailed discussion of EDCs and their proposed mode of action as possible reprotoxins and concludes that even, when the possibility of endocrine disrupting mode of action is taken into account, the adequate default position is that there are thresholds for reprotoxic effects for nearly all relevant substances.

The majority opinion of the experts and authorities seems to be that thresholds for induction for sensitisation do exist, health-based reference values based on the threshold assumption can likely be determined (despite some methodological difficulties) for skin sensitisers only. For respiratory sensitisers, thresholds for adverse effects (induction of sensitisation) exist, but – with currently available models and methods - are difficult to determine, and a non-threshold approach may thus be a more practical approach to controlling risks from occupational exposure.

[75] These are effects caused by skin contact and the standard setting is typically done at the workplace for inhalation exposure only.

Part B: The Burden of Ill Health Under the Baseline

B1 Introduction to Part B

B1.1 Summary

This Part of the report presents estimates of the current burden of occupational ill-health arising from worker exposures to Reprotoxic 1A and 1B substances not also classified as Carcinogens or Mutagens 1A/1B. This includes estimates of the number of cases of different types of health effects, and how these are measured in terms of Disability Adjusted Life Years (DALYs). The outputs therefore relate to Sub-tasks 2.2 and 2.13 of the study (see the Introduction for further discussion of the full set of tasks comprising the research).

In preparing these estimates, the study team drew on the work carried out under several of the other tasks. They either provided outputs which fed directly into the derivation of the estimates of the burden of disease, or provided important context for derivation of these estimates. This includes:

- Sub-task 1.1: Regulatory systems at the EU, MS, EEA and competitor country levels;
- Sub-task 1.3: Identification of strategic approaches;
- Sub-task 2.1: Development of a list of Reprotoxic 1A and 1B substances;
- Sub-task 2.3: Identification of groups of chemicals of particular concern;
- Sub-task 2.4: Overview of risk management measures;
- Sub-task 2.6: Overview of voluntary industry initiatives; and
- Sub-task 2.7: Assessment of existing and planned regulatory actions.

The remainder of this introductory section provides a general introduction to the approach taken to estimating the burden of health effects. In so doing, it also provides a brief discussion of how we drew on the above sub-tasks in developing the estimates. It is then followed by reporting on the estimates of the burden of ill-health resulting from occupational exposures to Reprotoxic 1A and 1B substances that are not also classified as Carcinogens or Mutagens 1A/1B.

B1.2 Overall approach to estimating the burden of health effects

B1.2.1 Summary

The research adopted two different approaches towards predicting the current burden of health effects associated with occupational exposures to Reprotoxic 1A/1B substances. These estimates provide the baseline for the impact assessment of the future policy options and have been derived through the use of two different methods:

7. The first method involves adopting a **top-down** approach, drawing on the use of population level incidence and prevalence data for health effects linked to exposures to reprotoxic substances. These prevalence data are adjusted to derive the potential maximal burden of effects that could be attributed to occupation exposure.

8. The second method is based on a **bottom-up** approach. It develops estimates for a set of shortlisted Reprotoxic 1A/1B substances. For these selected substances, dose-response relationships for different effects identified from the toxicological literature for those substances have been developed. These have then been combined with data on uses, exposures (including from monitoring data), and numbers of workers likely to be exposed based on Eurostat data.

Section B2 of this part provides the results of the top-down approach while Section B3 provides the bottom-up estimates for individual/groups of substances identified as being of particular concern. The full results for each of these substances/substance groups, together with the underlying data used for their estimation, are provided in Annexes 10-21. Section B3 also provides indicative extrapolation to the remaining Reprotoxic 1A/1B substances not covered by the set of shortlisted substances discussed in the Annexes. This extrapolation therefore provides a second estimate for comparison against the top-down estimate. The economic value of the predicted burden of ill health under the baseline is then presented in Section B4 for both the bottom up and top down approach.

The results from both approaches are affected by several uncertainties, and a summary of the key differences are provided below. As the top-down approach relies on incidence or prevalence rates in the general population, several adjustments to the data are necessary. In particular, it is important to adjust the data for known non-occupational causes before applying the resulting incidence rates to the occupationally exposed population, as well as to ensure that the population taken into account is of reproductive age; similarly, for developmental effects, it is important to only consider the proportion of births born to women within the working population.

The bottom up approach reflects cases for which there is sufficient data and, consequently, it has the potential for underestimation. Dose-response functions can only be developed for the effects for which there are sufficient data in published scientific studies, measured exposure data may suffer from a positive bias, and linking effects analysed in published scientific literature with cases of reprotoxic ill health can be difficult. This approach thus provides an estimate of the number of cases for which there is sufficient 'evidence' that an effect seen in the laboratory translates to an effect in humans.

Note that for both approaches, we have also quantified the health burden in terms of the associated disability adjusted life years (DALYs) and/or using willingness to pay and cost of illness estimates.

B1.2.2 Comments and context to the estimates

It is important that the context underlying these two sets of estimates is clearly understood. In this respect the following aspects are important.

1. Both sets of estimates are based on a subset of Reprotoxic 1A/1B substances, however, they would also appear to capture substances expected to have the highest potential for worker exposures above the threshold for effects. In this respect, there are overlaps with both sets of estimates covering some of the key substances (e.g. lead, glycol ethers, DMF (Dimethylformamide) and DMAC (N,N-Dimethylacetamide) and NMP (N-Methyl-2-pyrrolidone) - see also Sections B2 and B3), with the bottom-up estimates in particular drawing on a "risk" screening process for this purpose (and the outputs of Sub-tasks 2-1 and 2.3). Importantly, both sets exclude Reprotoxic 1A/1B substances which may also be classified for carcinogenicity and mutagenicity.

2. As the aim of the assessment is to estimate the burden of ill-health that would be impacted by a change in policy, it is prospective and not retrospective. This means that some high profile Reprotoxic 1A/1B substances, such as the phthalates, should not really be taken into account. These have been subject to Authorisation under REACH[76], with this reducing manufacturing and industrial use and, hence, worker exposures; further Restrictions are proposed (not for worker protection reasons but) to reduce consumer exposures. However,

[76] The most recent Applications for Authorisation under REACH were found to demonstrate adequate control with respect to worker exposures, i.e. exposures were below the threshold for effects.

for the top down assessment such adjustments have not been made to the Sumer data so as to provide conservative estimates. In contrast, the bottom-up assessment takes into account the fact that some of the most high profile Reprotoxic 1A/1B substances have already been subject to regulation under REACH (i.e. the phthalates, NMP, etc.) and that further measures are currently proposed (REACH Restrictions) or are likely to come into effect (REACH Authorisation). They also take into account differences in regulation of the substances at the Member State level (drawing on Sub-task 1-1).

3. Both sets of estimates start by considering the entirety of the potentially exposed population to Reprotoxic 1A/1B substances not also classified for carcinogenicity and mutagenicity, and then adjust the population downwards in order to reflect reported or predicted exposure levels. For example, the top-down approach considers the intensity and the duration of exposures as reported in the Sumer survey. The bottom-up approach is based on more reliable, substance specific data. It uses monitoring data provided by relevant industry sectors for the purposes of this study, as well as published data and data provided in the Chemical Safety Reports for the different substances[77]. Thus, risk management measures (Sub-task 2.4) and industry strategic initiatives are also taken into account where appropriate and reflected in the baseline bottom-up estimates (Sub-tasks 1.3 and 2.6 - with the International Lead Association's (ILA) Lead Action 21 being the main example). Failure to consider the level/intensity of exposures together with duration would result in the burden of ill-health due to occupational exposures being overestimated.

4. The population adjustments start by separating out the populations by sex (male and female), percentage of population of reproductive age, percentage of population likely to be trying to conceive a child, percentage of the female population pregnant/giving birth to a child on an annual basis. These adjustments are made to ensure that impacts are being assessed across the most appropriate populations. The effect of these is to reduce downwards the number of relevant workers of concern from a starting population figure. Without such adjustments the burden of ill-health due to occupational exposures would be overestimated.

5. The top-down estimates are based on combining aggregate data on the population predicted as being potentially exposed at intensities and durations of relevance based on exposures to a subset of Reprotoxic 1A/1B substances with data on the attributable fractions (AF) of health effects for the general population. No adjustment is made to the top down estimates to take into account the health effects specific to the group of substances on which the estimates are based. As a result, the top-down approach may over-predict some health outcomes and under-predict others. The extent of the bias is unknown. There are other aspects of these estimates that may lead to under- or over-estimates, and these are discussed further in Section B2.

6. The bottom-up estimates are based on dose-response functions and on long-term exposure levels, rather than shorter duration or peak exposures. This was the only feasible approach given the nature of the available data. This may result in an underestimate if exposures if short duration exposures could lead to reprotoxic effects.

[77] Provided in the strictest confidentiality by ECHA.

B1.3 List of relevant reprotoxic effects

As context for the burden of ill-health estimates presented in B2 and B3, it is important to have an understanding of what types of effects were considered by this study. The starting list for the potentially relevant set of reprotoxic effects to be considered in the study were identified from EU-wide statistical sources and from the toxicological data available for the sub-set of Reprotoxic 1A/1B substances examined as part of the bottom-up analysis in more detail.

The main EU-wide sources for developmental effects were the Eurocat[78] database which provides prevalence rates for the number of births with congenital anomalies, excluding genetic factors. In addition, data are taken from Euro-Peristat for perinatal health (e.g. infant mortality, birth weight distributions). In addition to these, a range of other sources has been drawn upon which identify effects including infertility, spontaneous abortions, miscarriages, reduced IQ levels, etc.

With respect to the reproductive effects identified through the toxicological literature review, these were identified by expert toxicologists. The full list of effects is given in Annex 6. From these, only those that corresponded to the potential for human health effects and for which there are sufficient data to determine a threshold for reproductive effects were selected. No determination was made at this stage as to whether there was any evidence of exceedance of the relevant threshold. The full list of potential effects identified as being relevant

Combining these sources leads to the effects listed in Table B1-1, with this acting as the starting set of potential effects within the baseline or current burden of ill-health. As can be seen from this table, a larger set of potential effects was taken into account in the top-down assessment (using attributable fractions) than in the bottom-up analysis, due to the inability to link all toxicological effects to relevant effects in humans.

It should be noted that not all congenital anomalies reported to Eurocat were considered by the research team to relevant to exposures to reprotoxins. The decision to exclude a particular health effect was made by an experienced toxicologist with specialist knowledge of reprotoxins and reprotoxic effects. The difference in numbers is discussed further in Section B2.

Table B1-1: Summary of health effects considered potentially relevant as arising from workplace exposures

Eurocat, Euro-peristat, other EU-wide data sources	Toxicological studies
Fertility, fertilisation/implantation	
Infertility – male and female	Impaired fertility – male and female
	Impaired fertility – male offspring
Ectopic pregnancy	
Placenta previa	
Abruptio placenta	
Endometriosis	Endometriosis
Spontaneous abortion and miscarriages	Spontaneous abortion
Neo-natal, post-natal	
Stillbirth	Still birth
Perinatal death	
Infant death (including sudden infant death	
Preterm birth	
Low birth weight / Small for gestational age	Reduced foetal growth

[78] European surveillance on congenital anomalies – see http://www.eurocat-network.eu/

Table B1-1: Summary of health effects considered potentially relevant as arising from workplace exposures	
Eurocat, Euro-peristat, other EU-wide data sources	**Toxicological studies**
Congenital malformations	
Anencephaly	
Spina bifida	Spina bifida
Neural tube defects	
Hydrocephaly	
Eye defects	
Cardiovascular defect	Cardiovascular abnormalities
Congenital heart defect	
d-transposition of the great arteries	
Ventricular septal defects	
Atrial septal defects	
Atrioventricular septal defects	
Tetralogy of Fallot	
Hypoplastic left heart S.	
Patent ductus arteriosis	
Coarctation of aorta	
Outflow tract defects	
Cleft palate	Cleft palate
Cleft lip, w/out palate	Cleft lip
Anorectal atresia	Imperforate anus
Urinogenital defects	Urinogenital abnormalities
Cryptorchidism	Cryptorchidism
Hypospadias	Hypospadias
Clubfoot	
Limb deficiency	Skeletal abnormalities of the limbs
Craniosynostosis	
Gastroschisis	
	Renal abnormalities
Other	
Impaired cognitive development	Impaired cognitive development, e.g. IQ
Testicular cancer	Autism
	Attention deficit hyperactivity disorder
	Osteoperosis
	Obesity
	Diabetes
	Asthma

B1.4 Strategic approaches and best practice Risk Management

One of the aims of the research was to identify what types of approaches and measures are currently in place to control or reduce occupational exposures to Reprotoxic 1A and 1B substances not also carcinogens or mutagens. This information is of general interest to EU regulators but is also important, as discussed above, for setting the baseline level of ill-health that may be arising from occupational exposures. The results of this work (Sub-tasks 1.3, 2.4 and 2.6) are summarised in more detail in Annex 7.

The key findings are summarised here:

- Strategic approaches and voluntary initiatives: there are few concrete initiatives aimed at controlling or reducing occupational exposures to Reprotoxic 1A and 1B substances, highlighting a potential gap. There are various initiatives that may provide information of relevance (such as the European Surveillance of Congenital Anomalies (EUROCAT) network of population-based registries for the epidemiologic surveillance of congenital anomalies, and the HBM4EU human biomonitoring initiative) or that may help/encourage companies to take action to reduce exposures (e.g. the EU-OSHA Healthy Workplaces Campaign), but these are not targeted specifically at Reprotoxic 1A and 1B substances. The most specific initiatives apply at the national level (voluntary agreements and information campaigns) or at the sectoral level. With respect to the latter, the International Lead Association's (ILA) voluntary employee blood lead reduction programme, known as the Lead Action 21[79] programme, stands out, together with the European Lead Sheet Association's Product Stewardship Program[80] for reducing occupational exposure to lead.

- Risk management measures: as part of the bottom-up analysis, targeted consultation was carried out with companies in the industry sectors relevant to the group of Reprotoxic 1A and 1B substances identified as being of most concern (and expected to account for the most risks to workers). This identified several examples of good/best practice in eliminating and/or managing occupational risks to reproductive health by following the hierarchy of preventive and protection measures under the CAD and CMD. It also identified the other types of risk management measures that should be in place due to EU-wide or national Occupational Exposure Limit Values being place for the substances, as well as guidance on safe use under REACH. A key finding of this research is that many companies are likely to adopt measures in addition to those recommended in extended Safety Data Sheets, in response to the more onerous, general legal duty placed on them as employers under the CAD and CMD.

[79] International Lead Association (2018): LA21 Charter. Available at: https://www.ila-lead.org/responsibility/la21-charter

[80] European Lead Sheet Association (undated): Product Stewardship. Available at: https://elsia.org.uk/product-stewardship/

B2 Top-Down Estimates of the Burden of Ill-Health

B2.1 Introduction

This section summarises the potential burden of health effects associated with occupational exposures to Reprotoxic 1A/1B substances, as calculated using the top-down approach. This approach draws on the use of population level incidence and prevalence data, and attributable fractions, for the types of health effects linked to exposures to Reprotoxic 1A/1B substances. It combines these with estimates derived for the relevant worker population to calculate the potential maximal burden of effects that could be attributed to occupational exposures.

Key findings

The results of this assessment are as follows:

- A wide range of potential effects have been identified as being relevant to Reprotoxic 1A/1B substances, with these including impacts on male and female infertility, neo- and post-natal effects, as well as a range of congenital anomalies in newborn children. Exposures to reprotoxins are not the only risk factors for such effects, however, with other maternal and environmental factors including smoking, obesity and diabetes. In addition, it must be remembered that exposures to reprotoxins may not only occur in the workplace.

- Based on a 2010 self-reporting survey (the so-called Sumer survey) carried out on the French labour force:
    - 1.1% of workers self-reported that they were exposed to a selected group of Reprotoxic 1A/1B substances (lead, glycol ethers, phthalates NMP, DMF and DMAC) that are also not classified as carcinogens and mutagens;
    - Although this may represent the population that may be exposed, this does not mean that these workers are exposed at levels which would give rise to effects. Indeed, the data indicate that only a very small percentage of this 1.1% of workers is actually exposed at significant intensities (i.e. above the threshold for effects) and durations to the group of substances; thus, one would expect the potential for impacts to be very low;
    - Extrapolation up from the French data to the EU level and multiplied by two account for other Reprotoxic 1A/1B substances that are also not classified as carcinogens or mutagens leads to estimates that between 22,000 and 61,000 male workers (0.015 – 0.043%) and 3,000 and 8,000 female workers (0.003 - 0.007%)(based on geometric means and with and without welding) are anticipated as being exposed long enough and to levels that may be high enough to give rise to reprotoxic effects (i.e. at levels above the threshold for effects);

- Combining figures on the predicted EU population that may be exposed to Reprotoxic 1A/1B substances at levels that may give rise to effects, as well as adjusting for the percentage of women getting pregnant in any one year, results in the following estimated cases:
-
    - Fertility effects: between 39 and 1,055 cases of infertility or babies not being carried to term;
    - Developmental effects: between 7 to 219 cases of developmental effects.

Limitations

There are some important limitations to this top-down assessment. It is based on data for only one country and may therefore not be representative of worker exposures across the EU as a whole. It is also based on only a subset of Reprotoxic 1A and 1B substances not also classified as carcinogens and mutagens although, as discussed in Section B3 below, these include substances that are expected to account for the majority of workplace risks from exposure to reprotoxins. In addition, within the reported data, there are significant numbers of entries which are "not declared" or missing. The reasons for these could range from ignorance to a reluctance to report.

On the other hand, the top-down approach relies on incidence or prevalence rates in the general population and estimates the theoretical maximum number of cases by deducting known non-occupational causes and applying the resulting incidence rates to the occupationally exposed population. This approach relies on sufficient data being available for non-occupational causes and, as a result, entails a potential for overestimation. Adjustments have also been made to ensure that the population taken into account is of reproductive age; similarly, for developmental effects, it is important to only consider the proportion of births to women within the working population.

All of these adjustments lead to uncertainties. For example, it has not been possible to adjust the data for all known non-occupational causes of infertility and developmental effects, as such an approach would rely on the availability of specific attributable fraction data for those causes; this leads to the potential for overestimation.

B2.2 The approach

The top down approach draws on a range of different sources of information and involves several steps, as illustrated in Figure B2-1 below. The steps involved in developing the estimates can be summarised as follows:

1. Data were collected on the number of male and female workers in the EU. These were then adjusted for the percentage of the population of reproductive age, where this was taken as below 65 for men and between ages 15 and 49 for women.

2. Statistical data on numbers of live births and multiple births for EU women were used to calculate the number of couples trying to conceive in a given year. This was then combined with the percentage of couples experiencing infertility problems (14%[81], with roughly half due to male infertility and half due to female infertility), to generate estimates of: the number of male and female workers of reproductive age, the number births to female workers per annum, the number of worker-related infertility cases in a year for either men or women.

3. 2010 data available for France from the SUMER survey[82] were reviewed to establish predictions of the percentage of male and female workers that may be exposed to a significant effect to key reprotoxic substances. These data cover a broad range of industrial

[81] Wu A et al. (2012): Lead level in seminal plasma may affect semen quality for men without occupational exposure to lead. Reproductive Biology and Endocrinology, 10(1), 91

[82] Vinck L & Meemi S (2015): Les expositions aux risques professionnels les produits chimiques - Enquête Sumer 2010, available from: https://dares.travail-emploi.gouv.fr/dares-etudes-et-statistiques/etudes-et-syntheses/synthese-stat-synthese-eval/article/les-expositions-aux-risques-professionnels-les-produits-chimiques

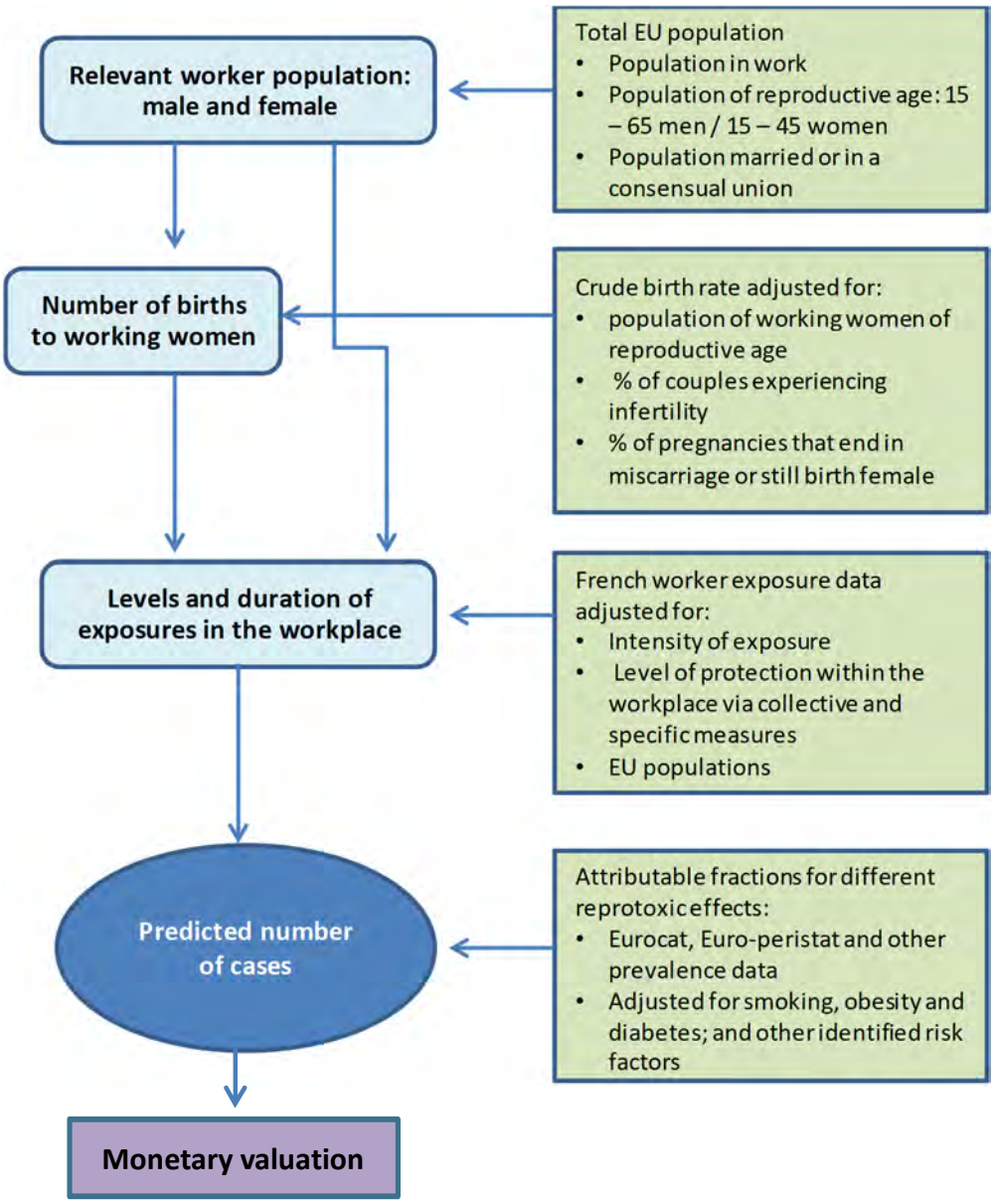

Figure B2-1: Overview of the top-down approach to estimating the burden of ill-health

and business sectors, and provide data for worker exposures in terms of duration and intensity of exposures to key reprotoxins. These data were used in combination to calculate the percentages of male and female workers potentially exposed to the substances at significant levels for extended periods.

4. Data were also collected on the incidence and prevalence of different health effects (albeit for the general population and for newborn children) which may be linked to exposures to reprotoxic substances. These incidence/prevalence data are adjusted for other risk factors as appropriate and where data are available (smoking, obesity, etc.), to develop rates that may better reflect the effects due to occupational exposures.

5. The above data are combined to develop overall estimates of the maximal burden of health effects in workers and their offspring that may be due to occupational exposures.

Because this top-down approach is based on attributable fractions that apply to the general population rather than attributable fractions for effects linked directly to occupational exposures to reprotoxic substances, it is likely to over-estimate the level of effects which stem solely from occupational exposures. This is why the approach is assumed to provide a set of maximal estimates that reflect an upper bound.

B2.3 Populations for the assessment

B2.3.1 Numbers of relevant workers in key industry sectors

Estimates for the numbers of workers in the key industry sectors are based on Eurostat data. From these, the following are estimated:

- The total number of women of working age (taken as 15-64) is around 170 million. 70% of these women are between the age of 15 and 49, reproductive age, with this equating to around 118.9 million women. 67% of these women are assumed to be in a consensual union;

- The total number of men of working age (taken as 15-74) is around 190 million. All of these men are assumed to be of reproductive age, with 67% also assumed to be in a consensual union.

B2.3.2 Births, trying to conceive and infertility

Based on Eurostat, within the EU around 5.06 million live births occur per annum, with an estimated 3% of these involving multiple births (mostly twins based on data for the UK, DE and NL). After accounting for multiple births, the implied number of conceptions is around 4.91 million per annum.

An estimated 85% of couples successfully have a live birth. The remaining 15% of couples may experience a miscarriage, spontaneous abortion or still birth. Based on the above data, we calculate that this equates to around 736,200 couples experiencing such a loss.

In addition to the above, roughly a further 14%[83] of couples may be affected by either male or female infertility, and therefore not be successful in conceiving. Combining this with the estimated number of couples having success in conceiving a child suggests that in any given year roughly 5.6 million couples are trying to conceive, with around 687,000 couples affected by either male or female infertility.

Not all of these cases of health effects are experienced by working women. Based on crude birth rates per head of female population (0.0198 total births, 0.010 male births, 0.0095 female births), the number of births to working women is around 3.36 million; this is roughly 66% of the total births.

These figures provide background context for the assessment.

[83] Wu A et al. (2012): Lead level in seminal plasma may affect semen quality for men without occupational exposure to lead. Reproductive Biology and Endocrinology, 10(1), 91.

B2.4 Data on exposures from the SUMER survey

B2.4.1 Introduction

There is presently only one study that determined (in part) the occupational exposure of workers to selected Reprotoxic 1A/1B substances, the so called "Sumer Survey"[84] which was carried out in 2010 and covered a broad range of industrial and business sectors, excluding extractive industries, coke refineries, extra-territorial activities, and household employment; it considered but with precaution public administrations and education. Within the different professions, 87 different job titles / positions were covered, ranging from unskilled to semi-skilled to skilled and administrative positions. Amongst a broader set of chemicals used in the workplace, the survey collected self-reported data on the number of workers exposed over different time periods and at different intensities to phthalates, 10 glycol ethers classified as Reprotoxic 1A or 1B (and a cat. 2), phthalates (including a non-Reprotoxic 1A and 1B phthalate), NMP, DMF and DMAC, and lead. This included self-reported data on the duration and intensities of exposures.

The results of this survey have led to an estimate that 1.1% of the French workforce is exposed to reprotoxic substances. As this is the only research that provides quantitative estimates/fractions of the worker population that is exposed to Reprotoxic 1A or 1B substances, which can be extrapolated to the entirety of the 28 MS, it is an important information source for this study. Thus, the Sumer survey data are analysed in detail below with various tables.

B2.4.2 Exposures to carcinogens, mutagens and reprotoxins from the Sumer Survey

The Sumer survey is based on a questionnaire given to 48,000 individuals, by 2,400 occupational and general medicine MDs. It is based on self-reporting, and many respondents did not provide the full set of information requested by the survey. As a result, it is difficult to interpret some of the data.

However, some of the headline estimates produced from the study provide important context for this study. Extrapolation of the survey results to the French workforce is based on the assumption that the workforce encompassed approximately 22 million workers at the time of the survey[85]. The sample ratio thus was approximately 48,000/22,000,000 or just over 0.2%, which is a reasonable ratio.

Analysis of the overall results by Cavet et al (2016) concludes that of the 22 million workers, 2,247,000 were exposed to CMR products (note this term and not "chemicals"). Of these:

- 2,181,000 were exposed to carcinogens (C);
- 184,000 were exposed to mutagens (M); and
- 234,000 (1.1%) were exposed to reprotoxins (R - with the scope including Reprotoxic 1A, 1B and 2 substances).

There obviously is some overlap in these figures, as illustrated in Figure B2-2 below. Adjusting for this overlap suggests that most of the workers indicating exposures to a reprotoxic substance also indicated exposure to a carcinogen and a mutagen (which can be assumed to overlap). Thus, the

[84] http://www.inrs.fr/dms/inrs/CataloguePapier/DMT/TI-TF-233/tf233.pdf

[85] Cavet, M et al., (2016). Les Expositions aux cancerogenes, mutagenes et reprotoxique: un zoom sur huit produits chimiques TF 233, INRS. At http://www.inrs.fr/media.html?refINRS=TF%20233

number of individuals who reported only be exposed to a reprotoxic substance equals 66,000 or around 0.3% of the French labour force.

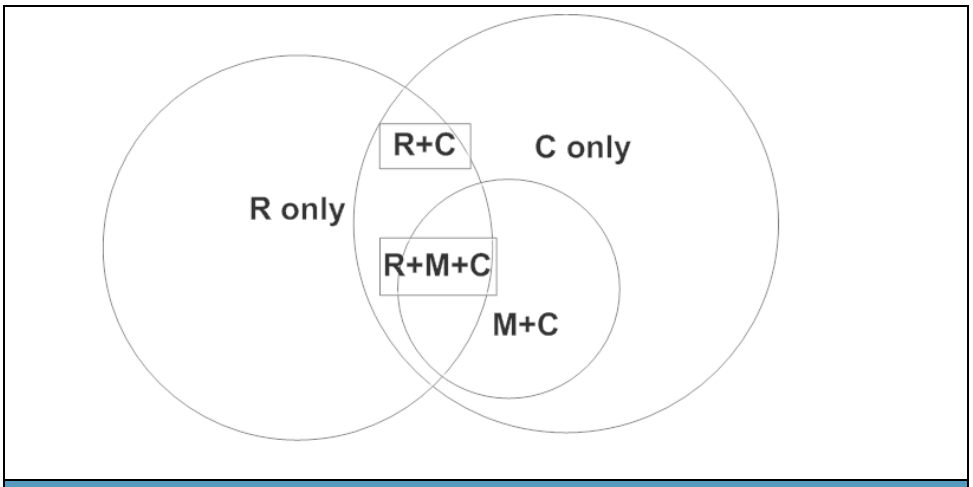

Figure B2-2: Overlaps in reported exposures to carcinogenic, mutagenic and reprotoxic "products"

A few interesting observations stem from this:

1. The data suggest that most workers exposed to a reprotoxic substance are also in work environments where they may experience combined exposures to other hazardous substances, in this case carcinogens and mutagens;

2. As a result, actions to control exposures to carcinogens and mutagens may also lead to low levels of worker exposure to reprotoxic substances. As detailed below, the Sumer survey data suggest this may be the case;

3. In such cases of combined exposure, the employer should have considered the potential for substitution of the carcinogen or mutagen under the CMD; he/she may or may not also have considered the potential for substitution of the reprotoxic substance.

As a result, although this figure provides valuable context, it is not taken forward as the basis for an estimate of the burden of ill-health that could be impacted by a change in the regulatory status of reprotoxins (i.e. if they were included in the CMD rather than remaining under the CAD).

Estimates based on the Sumer survey

Data on the duration of exposures and the intensity of exposures is taken from the survey to predict the percentage of the worker population that may potentially be exposed to reprotoxins at levels above a threshold for effects. As defined for this survey, very weak to strong exposure ranges from <50% of the OEL to >50% of the OEL but still below the OEL. Very strong exposure is at levels above the OEL.

Although the majority of reported exposures are "very weak" or "weak" with associated durations of "less than 2 hours" or "2-10 hours", there are a significant number of entries which are "not declared" or missing. The reasons for these could range from ignorance to a reluctance to report.

For the purposes of this analysis, missing and not declared values are assumed to be either low to give the 'best' case or high to give the 'worst' case.

The analysis for each chemical group is summarised below with the details provided in subsequent tables.

Phthalates

The figure for the number of workers exposed to phthalates is given as 58,100. Most workers were exposed for less than 10 hours per week and 78% or higher of the workers had exposures at a weak or very weak intensity. Importantly, the majority of these exposed workers recorded their employment as being within the health sector, social care sector, and infirmaries. As a result, their exposures are likely to be due to skin contact with medical devices (tubing, blood bags, etc.) which contain or were made using a phthalate (i.e. DEHP) and, due to the low durations and intensities of exposure, are unlikely to lead to risks of concern. Only 6,000 of the workers were employed in the fabrication of plastic products, and this figure will be an overestimate with respect to current exposures due to REACH Authorisation[86] and Restrictions. Some level of use may still exist in the manufacture of medical devices, but this should take place with exposures at levels below the threshold for effects. As a result, for the purposes of this assessment, it is assumed that 100% of workers are currently exposed at weak or very weak intensities.

Glycol ethers

Figures are also given for glycol ethers with reprotoxic properties, with an estimated 25,800 workers exposed. At least 85% were exposed for less than 10 hours per week and 77% (or more) had exposures at a very weak or weak intensity (less than 50% of the OEL concentration). Although some workers are protected by ventilation as a collective measure, at least 46% of workers do make use of personal protective equipment (gloves, respirators and goggles). Most of the exposed workers were involved in automotive repairs (motorcycles and cars). The majority of workers work for small and medium sized companies.

DMF and DMAC

Data are also provided for DMF (Dimethylformamide) and DMAC (N,N-Dimethylacetamide) with an estimated 33,200 workers. At least 90% were exposed for less than 10 hours per week and 65% (or more) had exposures at a very weak or weak intensity. Roughly half of the workers indicated that they were protected by collective measures including closed systems, ventilation and air exchange, with 77% also indicating that they made use of personal protective equipment. The majority of these workers worked for smaller and medium-sized enterprises in the pharmaceutical, scientific research and industrial chemicals sectors.

NMP

Data are provided for NMP (N-Methyl-2-pyrrolidone) with an estimated 47,700 workers. At least 80% were exposed for less than 10 hours per week and 67% (or more) at a very weak or weak intensity. 40% of the workers indicated that they were protected by collective measures including closed systems, ventilation and air exchange, with extensive use of personal protective equipment. NMP is

[86] Two of the three EU manufacturers have ceased production of DEHP; it is not known whether the third manufacturer is still producing DEHP. However, it is understood that the market no longer accepts the use of DEHP and the only authorised uses relate to unintended "use" when producing flexible PVC recyclate. The latest applications for this use were considered by the RAC to demonstrate adequate control. The proposed restriction on the presence of four phthalates in consumer articles, including DEHP, is aimed at protecting consumers and not workers.

used a solvent in a wide range of sectors including industrial chemicals, construction and car repair workshops.

Lead (not welding)

Lead and its use in alloys, battery manufacture, crystal, pigments and for repairing automotive radiators is linked to an estimated 115,300 workers. At least 75% were exposed for less than 10 hours per week and 78% (or more) had exposures at a very weak or weak intensity. At least 42% were provided with collective protection measures and a higher percentage at 74% with individual protective measures. Of the exposed workforce, only 13% was female, with the majority being in the age range of 25 to 49 years old, and fairly evenly spread throughout this age range. Interestingly, the two largest segments of this population were involved in construction (27,200 workers) and manufacture of batteries (16,100 workers), with alloy manufacture and metallurgical activities accounting for a further 11,000 workers. Some of the figures raise questions with regard to the uses actually taking place, for example, 2,600 workers indicate that they are exposed in the fabrication of electrical equipment; this is despite the fact that the use of lead solder was banned in the use of electrical and electronic equipment under RoHS in 2006.

Lead (via welding)

Welding of metals may release harmful fumes, vapour and particulates (smoke). The Sumer data indicate that 573,900 workers may be so exposed. It has been assumed that 20% of these workers (119,520) may be exposed to lead released during welding operations and that the general data presented applies equally to this subset of workers.

The Sumer data also indicate that at least 75% were exposed for less than 10 hours per week and 70% (or more) had exposures at a very weak or weak intensity.

At least 46% were provided with collective protection measures and a high percentage with individual protective measures. Of the exposed workforce, only 4% was female, with the majority of workers being older men.

Summary

A summary of key information extracted from the report is given in Table B2-1 below which was then used to generate data for two scenarios for the total number of workers that may be exposed to the different substances at levels which may potentially give rise to reprotoxic effects. For this purpose, the numbers of workers exposed to both strong/very strong exposures AND weekly durations in excess of 10 hours were derived. This leads to the first set of estimates - Scenario 1 - given in the table overleaf.

It is important to note that exposures of a “strong” intensity would reflect exposures >50% of the OEL but still lower than the OEL. If consideration is also given to the presence of collective measures within the workplace, then a second set of lower estimates is derived (Scenario 2).

The next stage is to extrapolate from the 2010 data for the selected groups of chemicals in France to 2016 data for all reprotoxins across the EU-28. These scaled up estimates are presented in Table B2-1. The first step was to simply double the estimates from the previous table to cover the range of chemicals which could give rise to reprotoxic effects. In terms of scaling up from the Sumer data, it is worth noting that Sumer was based on a French working population of 21.5m (60% male and 40% female). The 2016 EU-28 working population is approximately 260m (55% male and 45% female). This leads to further scaling factors of 11.2 for males and 13.4 females. 1

Table B2-1: Derivation of Incidence of Worker Exposure to Reprotoxins based on SUMER Data of 2010									
Parameter			**Phthalates**	**Glycol ethers**	**DMF and DMAC**	**NMP**	**Lead (not welding)**	**Lead via welding**	**ALL**
Population at Risk									
A	Number of male workers		28400	18200	24800	33000	101800	*114760*	**320960**
B	Number of females workers		29700	7600	8400	14700	13500	*4760*	**78660**
C=A+B	**Total number of workers**		**58100**	**25800**	**33200**	**47700**	**115300**	***119520***	**399620**
A	**Males of reproductive age (all)**		28400	18200	24800	33000	101800	*114760*	**320960**
D1	**Females of reproductive age (<50)**	**worst**	22492	4625	6781	11187	12072	3851	**61007**
D2		**best**	20192	3134	6553	10231	10397	3186	**53694**
E	% within marriage/consensual union		67%	67%	67%	67%	67%	67%	**67%**
F=A*E	**Males at risk**		**18943**	**12139**	**16616**	**22110**	**68206**	***76889***	**214988**
G1=D1*E	**Females at risk**	**worst**	**15002**	**3099**	**4543**	**7945**	**8088**	***2580***	**41325**
G2=D2*E		**best**	**13468**	**2010**	**4391**	**6855**	**6966**	***2135***	**35976**
Exposure									
H1	% Strong/Very Strong	worst	22%	23%	36%	33%	22%	30%	**27%**
H2		best	0.1%	0.3%	0.2%	0.2%	4.6%	14.1%	**5.6%**
Duration (hours/week)									
I1	% >10 hours	worst	44%	14%	8%	18%	24%	25%	**25%**
I2		best	40%	0%	0%	0%	19%	23%	**18%**
Collective Protection									
J1	% without measures	worst	64%	78%	48%	61%	58%	54%	**59%**
J2		best	14%	43%	17%	28%	40%	34%	**31%**
Scenario 1:									
K1=F*H1*I1	N males (Strong/Very strong)	worst	0 (see text)	389	462	1319	3512	*1140*	**6822**
K2=F*H2*I2	AND >10 hours	best		0	0	0	603	*508*	**1111**
M1=G1*H1*I1	N females (Strong/Very strong)	worst		99	126	447	416	*38*	**1126**
M2=G2*H2*I2	AND >10 hours	best		0	0	0	62	*14*	**76**
Scenario 2 with measures:									
O1=K1*J1	N males (Strong/Very strong)	worst	0 (see text)	305	220	803	2050	*124*	**3502**
O2=K2*J2	AND >10 hours AND No measures	best		0	0	0	239	*34*	**273**
Q1=M1*J1	N females (Strong/Very strong)	worst		77	60	272	243	*4*	**656**
Q2=M2*J2	AND >10 hours AND No measures	best		0	0	0	24	*1*	**25**

Table B2-2: Scaling up from France (2010) to EU (2016)						
Scenario		France (2010)		EU (2016)		
		Table 2-1	Doubled	Incidence	Rounded	% Workforce
Scenario 1 (strong/very strong exposure AND >10 hrs exposure)						
Males	Best (Low)	1,111	2,222	24,883	25,000	
	Worst (High)	6,822	13,644	152,729	153,000	
				Geometric Mean	**61,000**	**0.043%**
Females	Best (Low)	76	151	2,031	2,000	
	Worst (High)	1,127	2,254	30,222	30,000	
				Geometric Mean	**8,000**	**0.007%**
Scenario 2 (strong/very strong exposure AND >10 hrs exposure AND no collective measures)						
Males	Best (Low)	273	547	6,122	6,000	
	Worst (High)	3,486	7,004	78,399	78,000	
				Geometric Mean	**22,000**	**0.015%**
Females	Best (Low)	25	51	680	1,000	
	Worst (High)	657	1,315	17,624	18,000	
				Geometric Mean	**3,000**	**0.003%**

The resultant calculations (see Table2-2) suggest that, when taking no account of collective measures (Scenario 1), around 8,000 women (from the range 2,000 to 30,000) and 61,000 men (from the range 25,000 to 152,000) may be exposed to reprotoxins at levels which might be regarded as significant (even if still below the OEL). If collective measures are accounted for (Scenario 2), around 3,000 women (from the range 1,000 to 18,000) and 22,000 men (from the range 6,000 to 78,000) may be exposed to reprotoxins at levels which might be regarded as significant (even if still below the OEL).

It is important to restate that these estimates are based on uncertain data (with significant portions of the data missing) and, as such, are based on taking the geometric mean of the 'best' and 'worst' cases. To put these figures into context, 8,000 women represent less than 0.01% of the female EU workforce while 61,000 men represents around 0.04% of the male EU workforce. These figures are significantly lower than the figure of 1% of workers with any exposure to reprotoxins quoted by INRS.

These figures are used in the remainder of this top down analysis as the starting populations for estimating the potential number of female and male fertility related cases of reprotoxic effects using the collected incidence and prevalence data. We also use these data to adjust estimates of the percentage of children born with developmental effects for those that can potentially be attributed to worker exposures.

B2.5 Incidence and prevalence data

B2.5.1 Use of Attributable Fractions

As discussed in Section B2.2, the top-down approach draws on the use of attributable fractions (AF). The AF can be estimated if there is available data on the prevalence of a risk factor and the relative risk of a disease or outcome associated with that risk factor (Smith, Corvalán and Kjellström, 1999; Trasande *et al.*, 2016):

$$AF = \frac{Prevalence_{risk\ factor}(RR-1)}{1 + Prevalence_{risk\ factor}(RR-1)}$$

Where RR is the relative risk of a health effect (morbidity) associated with exposure to a chemical agent (Trasande *et al.*, 2015).

Therefore, in order to establish AFs for reprotoxic effects from occupational exposures to chemicals, the literature was searched for epidemiological studies giving data on:

- Prevalence of risk factors (e.g. exposure to chemicals, smoking, diabetes, obesity, genetic); and
- Relative risks / odds ratios for outcomes associated with the risk factor (exposure).

The AFs can then be used to calculate the "fractional contribution" of a risk factor to causation of an outcome (reproductive effects or birth defects), using the following equation (Institute of Medicine, 1981):

$$Attributable\ disease\ burden = Outcome\ prevalence \times AF \times Population\ size$$

B2.5.2 Data sources

Eurocat data

Data from the European Surveillance of Congenital Anomalies (EUROCAT) provides the basis for calculating the number of congenital anomalies that may occur as part of the developmental effects stemming from workplace exposures. Eurocat is a network of population-based registries for the epidemiologic surveillance of congenital anomalies. The network consists of 43 registries across 23 countries and covers 29% of the European birth population (with more than 1.7 million births surveyed per year in Europe).[87] The Eurocat data provides information on the prevalence rates for congenital anomalies both including and excluding genetic conditions per 10,000 births.

The Eurocat data covers over 80 different types of congenital anomalies, broken into different categories. Data may be reported against a category heading (e.g. eye) or against a specific anomaly (e.g. congenital glaucoma). In addition, as indicated in the technical notes to the data, children born with multiple anomalies may be recorded multiple times within the database, as Eurocat recommends recording up to eight malformations; in contrast, defects that are seen as consequences of other defects i.e. "sequences" (e.g. hydrocephaly when associated with spina bifida) are counted only under the primary defect in EUROCAT. As a result, there is a double counting of the number of children born with anomalies, but it is not easy to determine to what extent. However, the technical notes also stress that there may be underreporting due to a range of factors.

Data from Eurocat for 2012 to 2016 report on 69,457 cases of congenital anomalies excluding genetic conditions; this equates to around 13,900 cases per annum. Of these, the anomalies, or health effects considered as relevant to this study (31) account for 54,400 cases, or 78% of cases[88]. Those types of effects not take forward were screened from the assessment by toxicologists as being unlikely or not linked to exposures to Reprotoxic 1A/1B substances.

Euro-Peristat

In addition, data were drawn from Euro-Peristat[89] as appropriate to provide perinatal prevalence data. Euro-Peristat provides data on the health and health care of pregnant women and newborns and was

[87] EUROCAT (n.d.): What is EUROCAT? Available at: http://www.eurocat-network.eu/aboutus/whatiseurocat/whatiseurocat

[88] Although the analysis provided here was based on data up to 2015 (the 2016 data was not available at time of extraction), cross-comparison indicates that the prevalence rates are in most cases identical or vary by tenths of a case per 10,000 births.

[89] https://www.europeristat.com/

established as part of the EU's Health Monitoring Programme and covers 31 countries across Europe. It collects data on fetal mortality rates, neonatal mortality rates, infant mortality rates and birth weights, as well as a range of maternal indicators.

Other sources

A range of other sources of information have also been drawn on and which are too numerous to report on individually here (see references). These include references from the epidemiological and health literature, as well as various statistical sources. For example, Eurostat data on live births and multiple births, as well as World Health Organisation data on foetal deaths per 100 births.

The full list of effects taken into account are given in Table B2-4 at the end of this Section.

B2.5.3 Adjustments to incidence and prevalence data

Clearly, not all of the cases of anomaly or ill effects will be due to exposures to reprotoxic chemicals, and not all that are due to reprotoxic chemical exposures will stem from occupational exposures. As a result, a search of the literature was conducted to establish what epidemiological evidence there is on the number of cases of fertility, developmental and neo-natal/post-natal effects may be due to risk factors other than occupational exposures. By adjusting the Eurocat, Euro-peristat and other prevalence data for these other risk factors, the population attributable fraction (AF) more likely due to occupational exposures can be derived (Agopian et al., 2013).

Fertility and maternal impacts

Fertility effects may result from multiple risk factors, including genetic, dietary and behavioural, and environmental. The following fertility/maternal impacts were identified as of importance in terms of their incidence/prevalence within the general population (occupationally and non-occupationally exposed):

- Impacts on male infertility, with low sperm quality or quantity linked to about 7% of males when trying to conceive;
- Impacts on female infertility, which may include both primary infertility (around 1% of females) and secondary infertility (around 10.5% of females);
- Ectopic pregnancies, placenta previa and abruptio placentae with these affecting around 6.6% of females;[90]
- Endometriosis with an incidence of around 0.1% of women per annum and is reported as affecting between 1% and 15% of women; and
- Spontaneous abortions, miscarriages and still births with this affecting around 13.5% of women.

These general population incidence/prevalence data are combined with the above estimates of the number of male and female workers within the working population that may be exposed to Reprotoxic 1A/1B substances.

Because the causes of fertility-related effects are multifactorial, however, we have adjusted for the attributable fractions of cases associated with smoking, diabetes and obesity (BMI > 30). These are identified as common risk factors for both fertility and reproductive morbidity, with the assumed prevalence within the EU populations as set out in the table below.

[90] Ectopic pregnancy: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg21/

Table B2-3: Prevalence of risk factors in EU		
Outcome	**Prevalence (%)**	**Reference**
Smoking during pregnancy	11.8%	(Zeitlin, Mohangoo and Delnord, 2010)
Pre-gestational diabetes	1.3%	(International Diabetes Federation, 2017)
Pre-gestational obesity	13.4%	(Zeitlin, Mohangoo and Delnord, 2010)

Data for the prevalence of smoking during pregnancy and pre-gestational obesity are based on a European review conducted by Zeilin *et al.* (2010). The prevalence of pre-gestational diabetes is taken from the IDF Diabetes Atlas (2017) for women of childbearing age (20-39 yrs) in MS countries. As all data were country-specific, a weighted average was calculated to give an EU figure. The number of cases estimated for these additional risk factors is based on calculation of the attributable fractions linked to each of these risk factors, using relative risks / odds ratios from the literature, combined with Euro-Peristat (2010) and Eurostat data.

Developmental effects

The fractions of cases attributable to smoking during pregnancy, diabetes and obesity (BMI > 30) have also been estimated to calculate the maximum number of developmental effects cases that may be due to genetic or other environmental factors (not including the three risk factors of smoking, diabetes and obesity).

More generally, and excluding genetic factors, non-occupational risk factors may account for significant percentages of the various health effects. These include:

- Previous diseases and infections, including sexually transmitted diseases[91];
- Low folic acid, Vitamin A and Iodine intake and other dietary factors;
- Exposure to acetaminophen/paracetamol[92];
- Non-occupational environmental factors, including exposures to common air pollutants and endocrine disruptors;
- Non-occupational causes of sub-fertility.

Importantly, it should also be recognised that some effects may result from exposures to carcinogens and mutagens, and thus may not stem from exposure to Reprotoxic 1A/1B substances. Mutagens may affect reproductive capacity or lead to developmental effects including terata, and these substances would not necessarily be classified for reproductive toxicity. With respect to carcinogens, reproductive capacity and an offspring's health may be impaired if a substance leads to carcinogenic effects on reproductive organs (including breast, prostate, testis, ovarian and endometrial cancer). Also, genotoxic cancer effects at other tumour sites may indirectly affect reproductive health or the progeny (even if no germ cell mutagenicity has been demonstrated). Carcinogens with effects on reproductive organs or via a hormone-like MoA would not necessarily be classified for reproductive toxicity, as health and safety is sufficiently addressed from their classification for cancer.

Summary of adjustments factors

The AFs associated with the three factors and used in adjusting the prevalence data are presented in Table B2-4 below, for those effects for which they were identified. As can be seen from this table,

[91] https://academic.oup.com/aje/article/185/2/124/2857213

[92] Arendrup et al (2018)

these three risk factors can account for a significant percentage of the health effects also potentially relevant to occupational exposures.

Table B2-4: Summary of AFs for selected outcomes and key non-occupational risk factors			
Outcome	**Gestational smoking**	**Pre-gestational diabetes**	**Pre-gestational obesity**
Fertility, fertilisation/implantation			
Female infertility	6.6%		
Ectopic pregnancy	8.3%		
Placenta previa	6.4%		
Abruptio placenta	9.5%		
Pre-eclampsia		3.4%	18.4%
Spontaneous abortion	2.6%		4.0%
Neo-natal/birth effects, post-natal effects			
Stillbirth	5.2%	2.5%	7.8%
Perinatal death		2.6%	
Infant death			5.3%
Preterm birth	3.1%	0.6%	
Sudden infant death	21.9%		
Congenital malformations			
All major congenital malformations		3.9%	
Anencephaly			5.0%
Spina bifida			14.2%
Neural tube defects			10.4%
Hydrocephaly			8.4%
Eye defects	2.8%		
Cardiovascular defect	1.3%	3.7%	3.0%
d-transposition of the great arteries		4.9%	
Atrial septal defects	3.8%		4.5%
Atrioventricular septal defects	3.9%	11.5%	
Tetralogy of Fallot		7.0%	3.6%
Hypoplastic left heart S.		3.5%	6.4%
Coarctation of aorta		3.5%	3.1%
Cleft palate	2.5%		2.9%
Cleft lip, w/out palate	3.8%		1.7%
Anorectal atresia	2.3%		7.9%
Cryptorchidism	2.0%		
Clubfoot	3.0%		
Limb deficiency	3.0%		
Craniosynostosis	3.7%		
Gastroschisis	5.5%		

B2.6 Estimated numbers of cases of effects linked to occupational exposures

B2.6.1 Fertility and maternal effects

The resulting estimates for infertility related effects are set out in Table B2-5 overleaf. These set an upper bound on the number of cases that could be attributed to exposures to Reprotoxic 1A/1B substances (not also carcinogens or mutagens), as environmental factors excluding smoking, obesity

and diabetes as well as uncertainties as to the role of inherited conditions will be reflected in these estimates.

These maximal estimates for fertility should be interpreted with caution. It has not been possible to adjust the estimates for all of the known risk factors (such as sexually transmitted diseases) linked to the prevalence of e.g. female infertility, ectopic pregnancies, spontaneous abortions, etc. The estimates are also dominated by the calculated number of spontaneous abortions, followed by male and female infertility.

Note that these estimates take into account the fact that only 5.1% of women have a live birth per annum, that 15% of pregnancies do not go to term, and that around 14% of couples suffer from infertility.

B2.6.2 Developmental effects

With respect to developmental effects, data taken from Eurocat are for prevalence excluding known genetic factors. Even so, many of the endpoints are known to be associated with multifactorial risks related to genetic factors, previous diseases and infections, diet, environmental exposures, etc. For example:

- Pre-term births, still births, early neonatal deaths, etc. are likely to have multifactorial causes, which may or may not include exposure to a Reprotoxic 1A/1B substances;
- Neural tube defects, anencephalus, spina bifida, and hydrocephalus have been linked to exposures to Reprotoxic 1A/1B substances together with diet in some cases (e.g. a lack of folic acid and spina bifida and anencephaly);
- Similarly, hypospadias are linked to exposures to Reprotoxic 1A/1B substances exposures, in addition to genetic factors and the age of the mother.

Thus, although some adjustments have been made here for maternal smoking, diabetes and BMI>30 (as for fertility), accounting for these additional risk factors would clearly further reduce the maximal estimates.

Estimates of the number of cases of developmental effects arising from occupational exposures are given in Table B2-6.

The first set of estimates take as their starting point Eurostat data indicating that around 3.36 million children per year (out of a total of around 5.1 million births) are born to working mothers. However, it is clear from the Sumer data that only a small proportion of these children will have been born to working mothers occupationally exposed to Reprotoxic 1A/1B substances not also classified as Carcinogens and Mutagens 1A/1B.

Adjustments have been made to account for the fact that only a proportion of working women will be pregnant and give birth in any given year. Assuming that 96.3 million women are in work, are under the age of 50 and are in a consensual union then, based on the number of births to working women, around 5.1% of working women have a live birth in a year. Thus, the numbers of women exposed for the non-welding and welding related estimates given in Table B2-5 have been multiplied by 5.1% to calculate the numbers that may be pregnant in any given year. This equates to between 50 and 1,530 live births per year.

As can be seen from Table B2-6, it is estimated that for this number of live births, there may be between 7 and 219 cases of health effects based on the prevalence data given in the table. Care is required in interpreting this estimate of developmental effects attributable to occupational exposures, as it does not take into account the fact that there is clearly some overlap in the various health effects for which data are presented individually within the Eurocat database.

Given that the analysis of the Sumer data indicates that only between 1,000 and 30,000 women may be exposed at levels and for durations sufficient to give rise to developmental effects, these estimates appear reasonable, given that they also include adjustments for other known risk factors.

However, it has not been possible to include in these estimates any impacts on IQ from occupational exposures. These are substance specific and we cannot establish a more general means of deriving estimates; note that any such estimates may also be confounded by other risk factors such as iodine deficiency, which has been found to have a high prevalence in the EU (i.e. 57% of the population) and to give rise to IQ effects.

Finally, although the Sumer data account for exposures to only a sub-set of the Reprotoxic 1A/1B substances not also carcinogens or mutagens in use in the EU, the substances captured are also those considered to contribute to a significant percentage of the burden of exposures. In addition, as part of the extrapolation from the Sumer data, the number of workers exposed at significant levels has been doubled to account for other Reprotoxic 1A/1B substances not also carcinogens or mutagens, prior to multiplying up to the EU level. Based on the risk scoring exercise carried out to shortlist substances for further examination (see Section B3.4), the substances considered by the Sumer survey account for around 70% of risk.

Table B2-5: Prevalence and maximum numbers of fertility-related cases by health effect adjusted for smoking, diabetes and BMI (2016)* (note totals impacted by rounding)										
Fertility related effects linked to reproductive toxicity	Unadjusted Prevalence/ Incidence per 10,000	Number of cases based on adjusted prevalence data	Total attributed to smoking, diabetes and BMI>30	Maximum cases due to genetic, Repr and other risk factors	Number of cases based on adjusted prevalence data	Total attributed to smoking, diabetes and BMI>30	Maximum cases due to genetic, Repr and other risk factors	Number of cases based on adjusted prevalence data	Total attributed to smoking, diabetes and BMI>30	Maximum cases due to genetic, Repr and other risk factors
		Best case (excludes all missing values from the Sumer data)			Worst case (includes all missing values from the Sumer data at threshold for reporting as not significant – where NS <40)			Estimates based on geometric mean of worst and best case		
Scenario 1 = Including welding										
Secondary female infertility[1]	1,050	12	1	11	183	16	167	49	4	44
Ectopic pregnancy[2]	197	2	0	2	35	3	32	9	1	8
Placenta previa[2]	46	1	0	0	8	1	7	2	0	2
Abruptio placentae[2]	60	1	0	1	11	1	10	3	0	3
Endometriosis[2]	7	0	0	0	1	0	1	0	0	0
Spontaneous abortion and miscarriages[2]	1,320	15	1	14	232	21	211	62	6	56
Still births[2]	31	0	0	0	5	0	5	1	0	1
Male infertility[3]	700	102	0	102	628	0	623	252		252
Totals		**133**	**3**	**131**	**1098**	**43**	**1055**	**379**	**11**	**368**
Scenario 2 = excluding welding										
Secondary female infertility[1]	1,050	6	1	6	110	10	100	18	2	17
Ectopic pregnancy[2]	197	1	0	1	21	2	19	3	0	3
Placenta previa[2]	46	0	0	0	5	0	4	1	0	1
Abruptio placentae[2]	60	0	0	0	6	1	6	1	0	1
Endometriosis[2]	7	0	0	0	1	0	1	0	0	0
Spontaneous abortion[2]	1,300	8	1	7	139	13	127	23	2	21
Still births[2]	31	0	0	0	3	0	3	1	0	0
Male infertility[3]	700	24	0	24	317	0	317	90	0	90
Totals		**40**	**1**	**39**	**603**	**26**	**577**	**137**	**4**	**133**

Table B2-5: Prevalence and maximum numbers of fertility-related cases by health effect adjusted for smoking, diabetes and BMI (2016)* (note totals impacted by rounding)										
Fertility related effects linked to reproductive toxicity	Unadjusted Prevalence/ Incidence per 10,000	Number of cases based on adjusted prevalence data	Total attributed to smoking, diabetes and BMI>30	Maximum cases due to genetic, Repr and other risk factors	Number of cases based on adjusted prevalence data	Total attributed to smoking, diabetes and BMI>30	Maximum cases due to genetic, Repr and other risk factors	Number of cases based on adjusted prevalence data	Total attributed to smoking, diabetes and BMI>30	Maximum cases due to genetic, Repr and other risk factors
		Best case (excludes all missing values from the Sumer data)			Worst case (includes all missing values from the Sumer data at threshold for reporting as not significant – where NS <40)			Estimates based on geometric mean of worst and best case		
Notes: 1) *Incidence x exposed female population x % aged <49 x % consensual union (67%) x 5.1% x % fertility due to unknown factors* 2) *Incidence x exposed female population x % aged <49 x % consensual union (67%) x 5.1%* 3) *Incidence x exposed male population x % consensual union (62%) x % male infertility due to environmental factors x 5.1%* *Sources:* Eurostat; Skakkebeek, 2016; Neto 2016; Eurostat; George, 2006; Duckitt & Harrington, 2005; Wahabi et al, 2012; Augood et al, 1998; Castles et al, 2003; Ananth et al, 1993; Torloni et al, 2009; Wang et al, 2013; Molyneaux et al, 2014; Boots et al, 2011, also see Section 'references' for additional bibliography										

Table B2-6: Number of cases of effects in offspring of all working women of reproductive age, in a consensual union adjusted for the number of pregnancies per annum, and calculated as being exposed to potentially significant levels of reprotoxins										
Developmental effect linked to reproductive toxicity	Prevalence / incidence per 10,000 excl. genetic conditions	Number of cases excluding genetic conditions	Total attributed to smoking, diabetes and BMI>30	Maximum cases atttributed to exposure to Reprotoxins	Number of case based on adjusted EU data	Total attributed to smoking, diabetes and BMI>30	Maximum cases atttributed to exposure to Reprotoxins	Number of case based on adjusted EU data	Total attributed to smoking, diabetes and BMI>30	Maximum cases atttributed to exposure to Reprotoxins
		Best case (excludes all missing values from the Sumer data)			Worst case (includes all missing values from the Sumer data at threshold for reporting as not significant – where NS <40)			Estimates based on geometric mean of worst and best case		
Scenario 1										
Late neonatal death (7-27)	7.3	0.1	0.0	0.1	1.1	0.1	1.0	0.3	0.0	0.3
Perinatal death	48.5	0.5	0.0	0.5	7.4	0.7	6.8	2.0	0.2	1.8
Infant death	39.8	0.4	0.0	0.4	6.1	0.5	5.5	1.6	0.1	1.5
Preterm birth (<32 weeks)	10.8	0.1	0.0	0.1	1.7	0.1	1.5	0.4	0.0	0.4
Preterm birth (32-36 weeks)	63.5	0.6	0.1	0.6	9.7	0.9	8.8	2.6	0.2	2.4
Low birth weight (<1,500 g)	10.3	0.1	0.0	0.1	1.6	0.1	1.4	0.4	0.0	0.4
Low birth weight (<2,500 g)	69.8	0.7	0.1	0.6	10.7	1.0	9.7	2.8	0.3	2.6
Small for gestational age	1000.0	10.2	0.9	9.3	153.0	13.8	139.2	40.8	3.7	37.1
Neural tube defects	9.3	0.1	0.0	0.1	1.4	0.1	1.3	0.4	0.0	0.3
Anencephalus and similar	3.7	0.0	0.0	0.0	0.6	0.1	0.5	0.2	0.0	0.1
Spina bifida	4.6	0.0	0.0	0.0	0.7	0.1	0.6	0.2	0.0	0.2
Hydrocephaly	4.4	0.0	0.0	0.0	0.7	0.1	0.6	0.2	0.0	0.2
Eye defect	3.0	0.0	0.0	0.0	0.5	0.0	0.4	0.1	0.0	0.1
Congenital heart defect	65.4	0.7	0.1	0.6	10.0	0.9	9.1	2.7	0.2	2.4

Table B2-6: Number of cases of effects in offspring of all working women of reproductive age, in a consensual union adjusted for the number of pregnancies per annum, and calculated as being exposed to potentially significant levels of reprotoxins										
Developmental effect linked to reproductive toxicity	**Prevalence / incidence per 10,000 excl. genetic conditions**	**Number of cases excluding genetic conditions**	**Total attributed to smoking, diabetes and BMI>30**	**Maximum cases atttributed to exposure to Reprotoxins**	**Number of case based on adjusted EU data**	**Total attributed to smoking, diabetes and BMI>30**	**Maximum cases atttributed to exposure to Reprotoxins**	**Number of case based on adjusted EU data**	**Total attributed to smoking, diabetes and BMI>30**	**Maximum cases atttributed to exposure to Reprotoxins**
		Best case (excludes all missing values from the Sumer data)			**Worst case (includes all missing values from the Sumer data at threshold for reporting as not significant – where NS <40)**			**Estimates based on geometric mean of worst and best case**		
Severe congenital heart defect	18.7	0.2	0.0	0.2	2.9	0.3	2.6	0.8	0.1	0.7
d-transposition of great arteries	2.4	0.0	0.0	0.0	0.4	0.0	0.3	0.1	0.0	0.1
Ventricular septal defects	32.5	0.3	0.0	0.3	5.0	0.4	4.5	1.3	0.1	1.2
Atrial septal defects	13.7	0.1	0.0	0.1	2.1	0.2	1.9	0.6	0.1	0.5
Atrioventricular septal defects	2.0	0.0	0.0	0.0	0.3	0.0	0.3	0.1	0.0	0.1
Tetralogy of Fallot	2.8	0.0	0.0	0.0	0.4	0.0	0.4	0.1	0.0	0.1
Hypoplastic left heart S.	2.4	0.0	0.0	0.0	0.4	0.0	0.3	0.1	0.0	0.1
Patent ductus arteriosus	4.1	0.0	0.0	0.0	0.6	0.1	0.6	0.2	0.0	0.2
Coarctation of aorta	3.5	0.0	0.0	0.0	0.5	0.0	0.5	0.1	0.0	0.1
Outflow tract defects	15.9	0.2	0.0	0.1	2.4	0.2	2.2	0.6	0.1	0.6
Conotruncal defects	7.4	0.1	0.0	0.1	1.1	0.1	1.0	0.3	0.0	0.3
Cleft palate	5.1	0.1	0.0	0.0	0.8	0.1	0.7	0.2	0.0	0.2
Cleft lip, w/out palate	7.6	0.1	0.0	0.1	1.2	0.1	1.1	0.3	0.0	0.3

Table B2-6: Number of cases of effects in offspring of all working women of reproductive age, in a consensual union adjusted for the number of pregnancies per annum, and calculated as being exposed to potentially significant levels of reprotoxins										
Developmental effect linked to reproductive toxicity	**Prevalence / incidence per 10,000 excl. genetic conditions**	**Number of cases excluding genetic conditions**	**Total attributed to smoking, diabetes and BMI>30**	**Maximum cases atttributed to exposure to Reprotoxins**	**Number of case based on adjusted EU data**	**Total attributed to smoking, diabetes and BMI>30**	**Maximum cases atttributed to exposure to Reprotoxins**	**Number of case based on adjusted EU data**	**Total attributed to smoking, diabetes and BMI>30**	**Maximum cases atttributed to exposure to Reprotoxins**
		Best case (excludes all missing values from the Sumer data)			**Worst case (includes all missing values from the Sumer data at threshold for reporting as not significant – where NS <40)**			**Estimates based on geometric mean of worst and best case**		
Anorectal atresia and stenosis	2.8	0.0	0.0	0.0	0.4	0.0	0.4	0.1	0.0	0.1
Cryptorchidism	76.0	0.8	0.1	0.7	11.6	1.0	10.6	3.1	0.3	2.8
Hypospadias	17.4	0.2	0.0	0.2	2.7	0.2	2.4	0.7	0.1	0.6
Testicular cancer	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Clubfoot - talipes equinovarus	10.3	0.1	0.0	0.1	0.1	0.0	0.1	0.0	0.0	0.0
Limb deficiency (defects)	4.5	0.0	0.0	0.0	1.6	0.1	1.4	0.4	0.0	0.4
Craniosynostosis	2.3	0.0	0.0	0.0	0.7	0.1	0.6	0.2	0.0	0.2
Gastroschisis	2.5	0.0	0.0	0.0	0.4	0.0	0.3	0.1	0.0	0.1
Total statistical cases				**14.6**			**219.3**			**58.5**
Notes: Calculated as: *Prevalence/Incidence excluding genetic conditions x exposed population of pregnant mothers – (AFs for risk factors x exposed population of pregnant mothers)* Estimates based on Eurostat 2016 for number of live births, proportion of women working, proportion of women in a consensual union, proportion of women having a live birth, and percentage of births that are male.										

Table B2-7: Number of cases of effects in offspring of all working women of reproductive age, in a consensual union adjusted for the number of pregnancies per annum, and calculated as being exposed to potentially significant levels of reprotoxins										
Developmental effect linked to reproductive toxicity	Prevalence / incidence per 10,000 excl. genetic conditions	Number of cases excluding genetic conditions	Total attributed to smoking, diabetes and BMI>30	Maximum cases attributed to exposure to Reprotoxins	Number of cases based on adjusted EU data	Total attributed to smoking, diabetes and BMI>30	Maximum cases atttributed to exposure to Reprotoxins	Number of cases based on adjusted EU data	Total attributed to smoking, diabetes and BMI>30	Maximum cases attributed to exposure to Reprotoxins
		Best case (excludes all missing values from the Sumer data)			Worst case (includes all missing values from the Sumer data at threshold for reporting as not significant – where NS <40)			Estimates based on geometric mean of worst and best case		
Scenario 2										
Late neonatal death (7-27)	7.3	0.0	0.0	0.0	0.7	0.1	0.6	0.1	0.0	0.1
Perinatal death	48.5	0.2	0.0	0.2	4.5	0.4	4.1	0.7	0.1	0.7
Infant death	39.8	0.2	0.0	0.2	3.6	0.3	3.3	0.6	0.1	0.6
Preterm birth (<32 weeks)	10.8	0.1	0.0	0.1	1.0	0.1	0.9	0.2	0.0	0.2
Preterm birth (32-36 weeks)	63.5	0.3	0.0	0.3	5.8	0.5	5.3	1.0	0.1	0.9
Low birth weight (<1,500 g)	10.3	0.1	0.0	0.0	0.9	0.1	0.9	0.2	0.0	0.1
Low birth weight (<2,500 g)	69.8	0.4	0.0	0.3	6.4	0.6	5.8	1.1	0.1	1.0
Small for gestational age	1000.0	5.1	0.5	4.6	91.8	8.3	83.5	15.3	1.4	13.9
Neural tube defects	9.3	0.0	0.0	0.0	0.9	0.1	0.8	0.1	0.0	0.1
Anencephalus and similar	3.7	0.0	0.0	0.0	0.3	0.0	0.3	0.1	0.0	0.1
Spina bifida	4.6	0.0	0.0	0.0	0.4	0.0	0.4	0.1	0.0	0.1
Hydrocephaly	4.4	0.0	0.0	0.0	0.4	0.0	0.4	0.1	0.0	0.1
Eye defect	3.0	0.0	0.0	0.0	0.3	0.0	0.3	0.0	0.0	0.0
Congenital heart defect	65.4	0.3	0.0	0.3	6.0	0.5	5.5	1.0	0.1	0.9

Table B2-7: Number of cases of effects in offspring of all working women of reproductive age, in a consensual union adjusted for the number of pregnancies per annum, and calculated as being exposed to potentially significant levels of reprotoxins										
Developmental effect linked to reproductive toxicity	Prevalence / incidence per 10,000 excl. genetic conditions	Number of cases excluding genetic conditions	Total attributed to smoking, diabetes and BMI>30	Maximum cases attributed to exposure to Reprotoxins	Number of cases based on adjusted EU data	Total attributed to smoking, diabetes and BMI>30	Maximum cases atttributed to exposure to Reprotoxins	Number of cases based on adjusted EU data	Total attributed to smoking, diabetes and BMI>30	Maximum cases attributed to exposure to Reprotoxins
		Best case (excludes all missing values from the Sumer data)			Worst case (includes all missing values from the Sumer data at threshold for reporting as not significant – where NS <40)			Estimates based on geometric mean of worst and best case		
Severe congenital heart defect	18.7	0.1	0.0	0.1	1.7	0.2	1.6	0.3	0.0	0.3
d-transposition of great arteries	2.4	0.0	0.0	0.0	0.2	0.0	0.2	0.0	0.0	0.0
Ventricular septal defects	32.5	0.2	0.0	0.2	3.0	0.3	2.7	0.5	0.0	0.5
Atrial septal defects	13.7	0.1	0.0	0.1	1.3	0.1	1.1	0.2	0.0	0.2
Atrioventricular septal defects	2.0	0.0	0.0	0.0	0.2	0.0	0.2	0.0	0.0	0.0
Tetralogy of Fallot	2.8	0.0	0.0	0.0	0.3	0.0	0.2	0.0	0.0	0.0
Hypoplastic left heart S.	2.4	0.0	0.0	0.0	0.2	0.0	0.2	0.0	0.0	0.0
Patent ductus arteriosus	4.1	0.0	0.0	0.0	0.4	0.0	0.3	0.1	0.0	0.1
Coarctation of aorta	3.5	0.0	0.0	0.0	0.3	0.0	0.3	0.1	0.0	0.0
Outflow tract defects	15.9	0.1	0.0	0.1	1.5	0.1	1.3	0.2	0.0	0.2
Conotruncal defects	7.4	0.0	0.0	0.0	0.7	0.1	0.6	0.1	0.0	0.1
Cleft palate	5.1	0.0	0.0	0.0	0.5	0.0	0.4	0.1	0.0	0.1
Cleft lip, w/out palate	7.6	0.0	0.0	0.0	0.7	0.1	0.6	0.1	0.0	0.1

Table B2-7: Number of cases of effects in offspring of all working women of reproductive age, in a consensual union adjusted for the number of pregnancies per annum, and calculated as being exposed to potentially significant levels of reprotoxins										
Developmental effect linked to reproductive toxicity	**Prevalence / incidence per 10,000 excl. genetic conditions**	**Number of cases excluding genetic conditions**	**Total attributed to smoking, diabetes and BMI>30**	**Maximum cases attributed to exposure to Reprotoxins**	**Number of cases based on adjusted EU data**	**Total attributed to smoking, diabetes and BMI>30**	**Maximum cases atttributed to exposure to Reprotoxins**	**Number of cases based on adjusted EU data**	**Total attributed to smoking, diabetes and BMI>30**	**Maximum cases attributed to exposure to Reprotoxins**
		Best case (excludes all missing values from the Sumer data)			**Worst case (includes all missing values from the Sumer data at threshold for reporting as not significant – where NS <40)**			**Estimates based on geometric mean of worst and best case**		
Anorectal atresia and stenosis	2.8	0.0	0.0	0.0	0.3	0.0	0.2	0.0	0.0	0.0
Cryptorchidism	76.0	0.4	0.0	0.4	7.0	0.6	6.3	1.2	0.1	1.1
Hypospadias	17.4	0.1	0.0	0.1	1.6	0.1	1.5	0.3	0.0	0.2
Testicular cancer	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Clubfoot - talipes equinovarus	10.3	0.1	0.0	0.0	0.9	0.1	0.9	0.2	0.0	0.1
Limb deficiency (defects)	4.5	0.0	0.0	0.0	0.4	0.0	0.4	0.1	0.0	0.1
Craniosynostosis	2.3	0.0	0.0	0.0	0.2	0.0	0.2	0.0	0.0	0.0
Gastroschisis	2.5	0.0	0.0	0.0	0.2	0.0	0.2	0.0	0.0	0.0
Total statistical cases				**7.3**			**131.6**			**21.9**

Notes: Calculated as: *Prevalence/Incidence excluding genetic conditions x exposed population of pregnant mothers – (AFs for risk factors x exposed population of pregnant mothers)*
Estimates based on Eurostat 2016 for number of live births, proportion of women working, proportion of women in a consensual union, proportion of women having a live birth, and percentage of births that are male.

B3 Bottom-up Estimates of the Burden of Ill-Health

B3.1 Introduction

This section summarises the potential burden of health effects associated with occupational exposures to Reprotoxic 1A/1B substances not also carcinogens or mutagens, as calculated using the bottom-up approach. The estimates developed for this approach are based on detailed evaluation of a sub-set of 30 substances. Dose-response relationships and thresholds for different reprotoxic effects were developed for each substance and these were combined with data on levels of control in the workplace and the number of workers likely to be exposed to develop estimates of the potential burden of ill health.

Key findings

The results of the bottom-up assessment are as follows:

- In total, at the start of the study (March 2018), 194 substances were identified as Reprotoxic 1A/1B substances registered under REACH. After removing those also classified as Carcinogenic 1A/1B or Mutagenic 1A/1B (43 substances), those already restricted for reasons relevant to occupational exposures or going through Authorisation (12 non-CMR substances) and some self-classified substances, a long list of 52 fully registered/intermediate substances was developed. Substances in this list were prioritised based on consideration of risk (based on tonnages and Derived No Effect Levels), three aprotic solvents were added and a final list of 30 substances was developed.

- These substances may be used in 36 different industry sectors, with individual substances likely to be used in multiple sectors and many of the sectors being likely to use more than one of the substances;

- Data provided by industry (individual companies and associations), collected from CSRs and from the literature indicate that exposure levels are expected to be at levels below the thresholds for effects in most workplaces;

- Estimates for the number of workers that may be exposed to the 30 substances vary from around 1.5 million to 7.7 million depending on the assumptions underlying the exposure scenarios and whether lower or upper bound figures are taken, where ranges are available. These totals are maximal estimates as there is likely to be overlaps due to multiple substances being used within a single sector;

- After applying dose-response relationships and thresholds developed for each of the substances and different health effects (from information provided in the CSRs or SCOEL and RAC opinions), between 24 and 180 cases of reproductive ill health per annum were predicted as arising from exposures to the 30 substances and depending on exposure scenario. If theoretical (unrealistic) worst-case assumptions are taken, the figure rises to 1,429 cases.

Key limitations

The bottom up approach reflects cases for which there is sufficient data and, consequently, it has the potential for underestimation. Dose-response functions can only be developed for the effects for which there are sufficient data in published scientific studies, measured exposure data may

suffer from a positive bias, and linking effects analysed in published scientific literature with cases of reprotoxic ill health can be difficult. This approach thus provides an estimate of the number of cases for which there is sufficient 'evidence' that an effect seen in the laboratory translates to an effect in humans.

In addition, modelling for all substances (expect for lead) relies on air exposure data and dermal uptake is not modelled – this is likely to lead to underestimation of the effects. Whilst the extent of this underestimation is likely to be limited for some substances, there is insufficient evidence for some of the 30 substances to determine the extent of this underestimation.

B3.2 The approach

B3.2.1 Steps

The bottom-up approach draws on a range of different detailed sources of information and involves several steps, as illustrated in Figure B3-1. Broadly speaking, the work involved the following steps.

1. In total, 194 substances were identified as Reprotoxic 1A/1B substances registered under REACH. After removing those also classified as Carcinogenic 1A/1B or Mutagenic 1A/1B, some self-classified substances, most intermediates and NONS (due to a lack of data), as well as substances subject to Restrictions or Authorisation, a list of 52 fully registered substances and intermediates was developed. Substances in this list were prioritised based on consideration of risk (based on tonnages and Derived No Effect Levels), three aprotic solvents were added and a final list of 31 substances falling into six groups was developed.

2. Targeted consultation was undertaken with industry (Associations and companies), Member State Authorities, OSH practitioners and trade unions, in part to identify data on potential uses, exposures and worker populations exposed to the different substances.

3. REACH CSRs were obtained from ECHA under strict confidentiality, and were used together with information pulled from SCOEL and RAC opinions (including from Restriction dossiers) to act as the basis for information on:

    a. Uses of the substances of concern;
    b. Data on populations exposed, including estimates of the numbers exposed;
    c. Derived No Effect Levels (DNELs) for different health outcomes;
    d. Monitoring or other exposure data; and
    e. Recommended risk management measures.

4. Data were collated from the range of sources on the numbers of workers exposed, and then adjusted for the percentage of the population of reproductive age, where this was taken as below 65 for men and between ages 15 and 49 for women;

5. No effects thresholds and dose-response relationships were derived for all substances, for effects for which there is a human correlate and a means of quantification.

6. Exposure routes and levels for each substance were then assessed and effects that are not expected to occur under any of the scenarios considered in this study (including the theoretical worst-case scenario) were screened out, taking into account data on actual air concentrations and biomonitoring values.

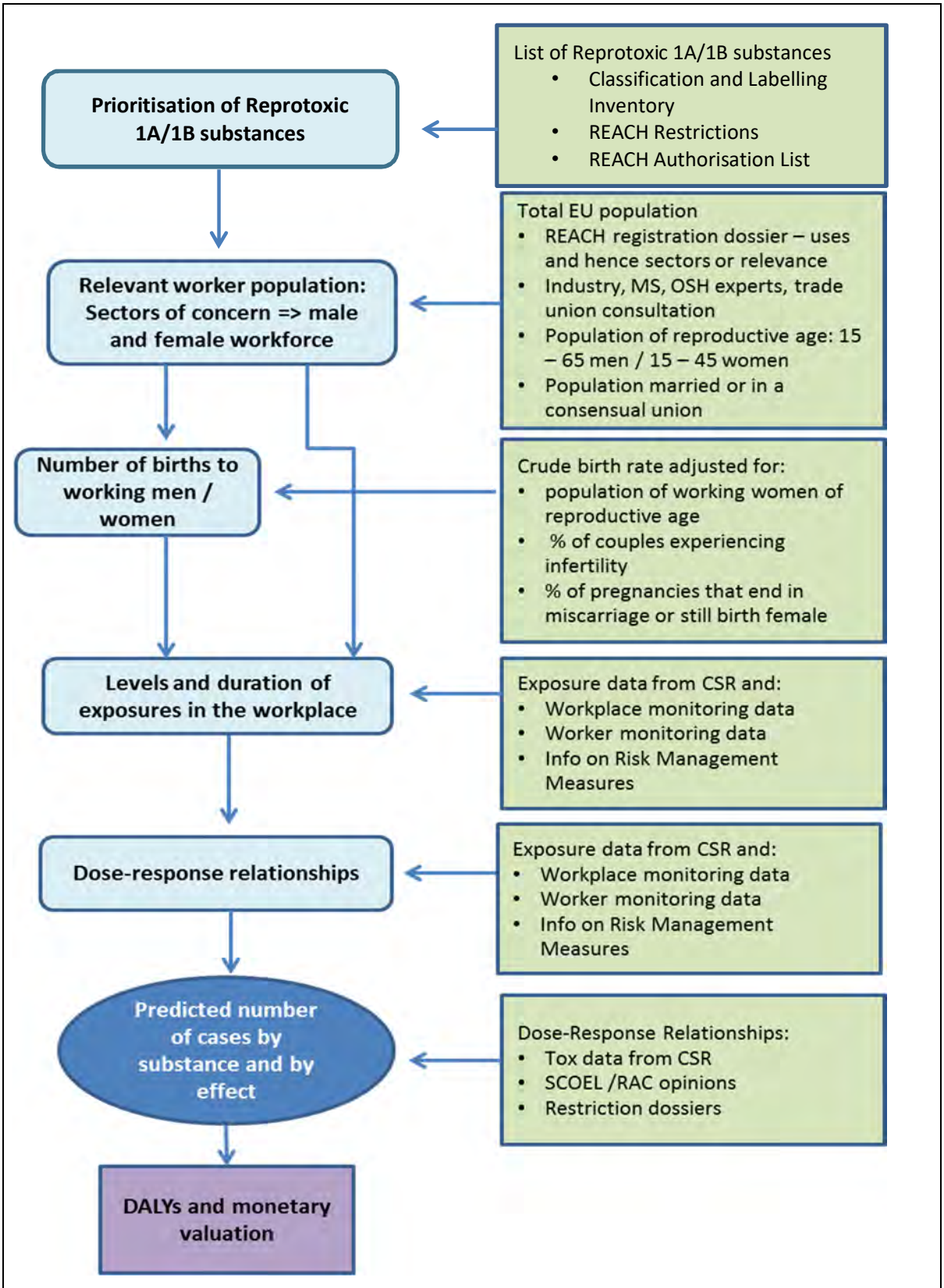

Figure B3-1: Overview of the bottom-up approach

7. The above data were combined to calculate the number of cases of reproductive ill health that may be occurring each year due to worker exposures to each of the substances. This burden is then translated into estimates of the number of associated Disability Adjusted Life Years stemming from this burden of ill-health.

The final estimates were then valued in monetary terms as part of the impact assessment work.

B3.2.2 Over and underestimation of the benefits and risks

Reprotoxic effects are just one of the effects that a chemical may cause. Other effects from chemicals can range from simple irritation to carcinogenicity, with there being no general rule as to what effects will occur at different levels of exposure. As part of the estimation of uncertainties, we endeavoured to qualitatively describe the impact from chemical exposure on endpoints besides reprotoxicity, as well as the overall uncertainty of our estimates.

This reports throughout uses our methodology to describe a group of 30 chemicals/subgroups as a starting point for estimating the reprotoxic effects from exposure to Reprotoxic 1A/1B (non C/M 1A/B) substances. This methodology has the potential to under- or over- estimate risks and, consequently, the benefits of the extension of the CMD to Reprotoxic 1A/1B substances due to, for example:

- methodological assumptions leading to overestimation of risk;
- underestimation of protective effect of reproductive thresholds and exposure associated minimization on other health effects;
- underestimation of total effects/risk from all Reprotoxic 1A/1B substances outside the CMD under the status quo due to undersampling of number of substances (30 out of >100)
- lack of accurate and up to date exposure data, leading to under or overestimation of exposure and hence risk; and
- occurrence of numerous reprotoxic effects at highly variable threshold levels.

Risk Management Measures (under both CAD and CMD but emphasised under CMD) both lead to decreases in exposure and so addition of Reprotoxic 1A/1B substances to CMD would not only reduce reproductive effects as intended, but also decrease all other possible effects such as systemic effects, and most likely sensitisation, at least for the less sensitive portion of the exposed population.

Given the trend of decreasing exposure concentrations in most workplace environments in the last years, it is also expected that exposure will decrease as well.[93] However, historical exposure data are taken as a proxy for actual exposures occurring today. Our "risk" estimates may therefore be overestimates[94].

In addition, our approach uses a linear interpolation between two exposure levels or assumes a NOAEL of 1/10th the LOAEL, in the absence of an actual NOAEL. Again, this approach is conservative, i.e. most likely to result in an overestimation of the actual slope or dose-response relationship. The latter approach also overestimates the NOAEL, i.e. it produces a smaller than realistic estimate for a threshold. Our approach is thus highly conservative when it comes to the estimation of threshold (exposure) levels and dose-response relationships.

[93] For example, discussion of future exposure to NMP. p121 in https://echa.europa.eu/documents/10162/f6cd9c0f-47b0-48d0-abfa-8e4224b3620e

[94] Given the paucity of exposure data available to us, we were forced to use historical data in the absence of more recent, published monitoring data.

On the other hand, there remains the question of how accurate our estimate of "risk" is for all Reprotoxic 1A/1B non-C/M 1A/1B substances, given that we only considered 30 chemicals/groups. In our selection process, we used DNELs and manufactured (registered) volumes as indicative surrogates of hazard and exposure and hence risk characterisation. Based on this methodology, we identified those chemicals accounting for around 90% of the risk characterisation score from all non R1/1B non-C/M 1A/1B substances. The uncertainty inherent to this surrogate risk screening is unquantifiable but is not expected to be that great, given the incorporation of around 90% of the risk characterisation.

We did not take into account Reprotoxic 1A/1B substances that are also for Carcinogens and Mutagens 1A/1B, although indicative extrapolation is provided. Carcinogenic (and mutagenic) thresholds where they exist are assumed to be (at least) as low as the reprotoxic threshold for a particular chemical. In cases where no threshold exists, closed systems/exposure minimisation should be employed, leading to reductions in exposure and hence risk. Thus, existing RMMs for Carcinogens and Mutagens 1A/1B should prove not only protective against carcinogenic effects but also against reprotoxic effects.

We also did not take into account Reprotoxic 2 substances. The evidence for relevant reprotoxic effects in humans is less clear for this group and it can be argued to some extent that highly potent substances would have gathered sufficient evidence to assign them to category 1. Therefore, it can be anticipated that the risk for such effects in humans is lower compared to category 1 substances. Thus, although we cannot ignore the risk contribution from Reprotoxic 2 substances, these contributions are less significant compared to the risk from R1 substances. It should also be noted here that Reprotoxic 2 substances were not within the scope of this project.

There are thus multiple indications that our approach could overestimate or underestimate hazard and exposure and hence risk, with limited exceptions.

Please note that the estimate does not take into account the (multiple) occurrences where effects such as carcinogenicity and sensitisation occur at lower exposure levels than reprotoxic effects. Such substances are already heavily regulated and the reduction of exposures to them would also reduce exposures related to their reprotoxic effects. For borates for instance, respiratory irritation may occur at levels at or below which the (weak) reproductive effects may occur. Protection of workers against respiratory irritation from borate exposure may thus act protectively against borates' potential reprotoxic effects. For NMP, the reproductive toxicity NOAEL is below the NOAEL for maternal toxicity. Hence protecting against reproductive effects would also protect against maternal toxicity.

The report generally focuses on a small number of reprotoxic effects from each individual chemical (group). Often many more effects were identified during our analysis but their magnitude is not known or it was not possible to translate from an effect seen in animals to humans. Both of these aspects add to the uncertainty. The reasons for this include, first of all, a lack of valuation data for some effects as noted throughout the report. Secondly and more importantly, the thresholds for these effects for a single chemical varied widely. Effects that have thresholds way above the exposure level hold much less significance and potential impact than those more proximate to the exposure level or in rare cases above or (very) near the OEL, especially if their dose-response slopes are equal or less than those seen for effects with lower thresholds. Further, it should be recognised that various reproductive toxicity endpoints observed for a specific substance are often mechanistically related, so should not be both taken into account.

In addition, some effects simply did not produce a "measurable or noticeable" effect at the population level. Thus, for borates, a decrease in birth weight only produced few cases going from normal to low birthweight, with less than one statistical case per year of very low/extremely low birth weight.

B3.3 Shortlisting substances and substance groups

B3.3.1 Aims of the shortlisting exercise

The aim of the shortlisting exercise was to establish a starting list of Reprotoxic 1A and 1B substances to act as the basis for establishing the baseline (Scenario 1) for the assessment of the potential future regulatory options for these substances. Thus, the intention has been to identify the Reprotoxic 1A and 1B substances which are anticipated as posing the greatest level of risk to worker populations, taking into account whether they would already fall under the CMD for carcinogenicity or mutagenicity, their tonnages and threshold for effects.

The starting point was therefore consideration of Reprotoxic 1A and 1B substances, as notified to ECHA's Classification and Labelling Inventory (CLI) and with additional consideration of REACH Registration data. Screening was then carried out to also identify substances which also held a classification for carcinogenicity and mutagenicity, were subject to REACH Restrictions or Authorisation, or were subject to regulation under other legislation such as the Plant Protection Products or Biocidal Products Regulations.

For Reprotoxic 1A and 1B substances which are used as intermediates only or are NONS (Notification of New Substances) substances, the necessary toxicological data and tonnage data were not always available. As worker exposure to intermediates should be limited, this should not result in a significant degree of under-estimation. Similarly, the number of NONS substances was small.

A risk ranking technique was then employed to select the list of Reprotoxic 1A and 1B substances to be evaluated in more detail, and to act as the basis for quantifying the burden of reprotoxic effects across the worker population.

This remainder of this sub-section summarises the approach and results of the screening process. For a more comprehensive overview, please refer to Annex 9.

B3.3.2 Approach

Key assumptions underlying the process adopted for this sub-task are as follows:

- As the focus is on future regulation of Reprotoxic 1A and 1B substances, the focus of Task 2 should also be on those reprotoxic substances that have not yet been subject to strict regulatory requirements;

- The above suggests that substances subject to REACH Restriction and Authorisation provisions should not be prioritised for calculation of the future burden of health effects (note that this condition is not also applied to the case studies, as the aim of them is to examine the interplay of regulation and what difference changes in regulation of Reprotoxic 1A and 1B substances would make compared to the current situation).

- Substances subject to Authorisation under REACH are also expected to be granted an Authorisation under conditions of strictly controlled use, with exposures limited to levels below the threshold for effects (which are assumed to exist for most of the Reprotoxic 1A and 1B substances which are not also carcinogenic or mutagenic;

- In addition, there are substances which are less interesting for understanding the potential burden of health effects under the baseline, because either they have not been registered

under REACH or their use is as an intermediate or because they are used in only very low quantities; such substances should therefore be given less priority compared to substances that have been fully registered under REACH and which have a wide range of potential exposures and uses; and

- The impacts of other regulations on potential worker exposures should also be taken into account, for example, where the default case is a prohibition on use such as applies under the Plant Protection Products and Biocidal Products Regulations.

Through this process a starting master list was narrowed down to a final set of substances for prioritisation. The starting list contained information on some 3,142 substances[95], of which 2,160 are not registered under REACH. In addition, most of these substances are based on a harmonised classification and the remainder are based on self-classifications from the CLI. It should be noted here that information on self-classifications from the CLI are drawn from the 'highest' level of classification in all notifications submitted to the CLI for a substance whether these are correct/accurate or not. As such, a proportion of the substances on the master list with a self-classification will not, in fact, be Repro. 1A or 1B or 2.

In total, 194 substances were identified as Reprotoxic 1A/1B substances registered under REACH. Removing those that were also classified as Carcinogenic 1A/1B or Mutagenic 1A/1B left 149 substances. Additional substances were removed as the lead REACH registrants had not self-classified the substance for Reprotoxin 1A/1B. This yielded a final set of 101 fully registered (62) and intermediate substances (39). After removing intermediates from the list and substances that have also be subject to Restrictions or Authorisation, there were 52 fully registered substances. See Annex 9 for further details.

A risk ranking approach was then applied to select the sub-set of substances to be prioritised for more detailed evaluation. This approach had to be based on readily available data. Since risk is commonly defined as the product of hazard and exposure, surrogates for both hazard and exposure were developed. Instead of Hazard Indices, we used a surrogate that was at hand and easily extracted from ECHA's databases, DNELs (Derived No Effect Levels). Given that DNELs are intended to represent the level below which risk cannot be measured/encountered it was chosen as the surrogate for health hazard. Exposure assessment generally starts by identifying the total quantity of a chemical which will be involved in the exposure, prior to more refined calculations. This quantity will usually drive the overall calculations. Hence, (the geometric mean of the) production volume (range) was used as a screening surrogate for exposure.

Tonnages for each of the substances were taken from REACH Registrations. The tonnage range was converted to a geometric mean (one significant digit); for example, a tonnage range of 10-100 tonnes was converted to 30 tonnes. DNELs (Derived No Effect Levels) were taken from REACH registrations and where no DNEL is available, a value of 1 has been used (see Annex 9).[96] Assigning a DNEL of 1 should not result in a missed selection as the only difference is in the partial risk contribution. Sensitivity analyses showed no differences in final selections, based upon our selection of a default DNEL value of 1.

[95] Data extracted in March 2018

[96] Usage of DNELs for overview, nominal risk estimates was endorsed by Eurostat, REACH Baseline study p10, https://ec.europa.eu/eurostat/documents/3888793/5844937/KS-RA-09-003-EN.PDF/351b1a93-fe8a-4085-8c67-4566fc8c6b48?version=1.0

For each classification category, substances with risk contributions greater than 1% have been selected in the final list of substances.

B3.4 The shortlisted Reprotoxic 1A/1B substances

Accounting for reprotoxins with a total group risk in excess of 1% of the class risk (classifications see below) resulted in clear distinctions. Chemicals that could be logically grouped, irrespective of their risk contribution, were also included such as lead compounds. These additional substances added little risk. Retinol and retinyl palmitate have also been selected for inclusion based on their distinctive dose response curve and also due to their classification as an essential nutrient/vitamin. Aprotic solvents were added at the request of the Commission at the time of the interim report.

In total, a shortlist of 30 substances has been selected for inclusion (see the table below).

Table B3-1: List of reprotoxins		
EC Number	**CAS Number**	**Name**
R1 Fully registered CLH RA		
201-245-8	80-05-7	4,4'-isopropylidenediphenol
231-100-4	7439-92-1	Lead
R1 Fully Registered CLH No RA		
200-679-5	68-12-2	N,N-dimethylformamide (DMF)
201-861-7	77-58-7	Dibutyltin dilaurate
201-861-7	88-85-7	Dinoseb
202-506-9	96-45-7	Imidazolidine-2-thione
202-696-3	98-73-7	4-tert-butylbenzoic acid
203-804-1	110-80-5	2-ethyoxyethanol
204-826-4	127-19-5	N,N-dimethylacetamide (DMAC)
206-104-4	301-04-2, 6080-56-4	Lead di(acetate)
211-670-0	683-18-1	Dibutyltin dichloride
212-828-1	872-50-4	1-methyl-2-pyrrolidone (NMP)
215-125-8	1303-86-2	Diboron trioxide
215-540-4	1303-96-4, 1330-43-4, 12179-04-3	Disodium tetraborate, anhydrous
233-139-2	10043-35-3	Boric acid
234-390-0	10332-33-9, 11138-47-9, 12040-72-1, 37244-98-7	Perboric acid, sodium salt
234-541-0	12008-41-2, 12280-03-4	Disodium octaborane
239-622-4	15571-58-1	2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate
310-154-3	121158-58-5	Phenol, dodecyl-, branched
R1 Fully Registered Self		
200-683-7	68-26-8	Retinol
201-228-5	79-81-2	Retinyl palmitate
201-289-8	80-54-6	2-(4-tert-butylbenzyl)propinolaldehyde
212-449-1	818-08-6	Dibutyl tin oxide
220-481-2	2781-10-4	Dibutyltin bis (2-ethylhexanoate)
235-252-2	12141-20-7	Trilead dioxide phosphonate
259-048-8	54261-67-5	Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate)
272-233-8	68784-25-8	Phenol, dodecyl-, sulfurized, carbonates, calcium salts
272-234-3	68784-26-9	Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased
272-486-4	68855-45-8	Phenol, dodecyl-, sulfurized, calcium salts
306-115-5	96152-43-1	Phenol, dodecyl-, branched, sulfurized

Within the set of 30 substances, there are six groups (and a further 6 substances falling outside these groups for a total of 12 substances/substance groups). These are (see also the table below):

- Borates (5 substances);
- Dodecyl compounds (6 substances);
- Lead compounds (3 substances);
- Retinol (2 substances);
- Tin compounds (3 substances); and

- Aprotic solvents (4 substances[97]).

Lead azide and lead 2,4,6-trinitro-m-phenylene dioxide have not been added to the shortlist of substances as it is unclear as to whether the health effects can be wholly accountable for by their identification as lead compounds or if this is offset by their reactivity. Omission of these two compounds constituted a negligible fraction of total lead production volume.

The list of 30 substances accounts for a calculated 97% (or higher) of the total risk score from chemical processing of Reprotoxic 1A and 1B substances, excluding carcinogens and mutagens, and NONS substances for which insufficient information is available[98]. The use of intermediates is covered as 4,4'-isopropylidenediphenol (BPA) has significant intermediate use. See also Annex 9.

In addition, four aprotic solvents were added to the list of substances to be evaluated at the request of the Steering Group for this study. The aprotic solvents are still in widespread use, although NMP in particular has been subject to Restrictions.

The group of substances considered here excludes the phthalates as those that have harmonised classifications as Reprotoxic 1A or 1B substances (DEHP, DBP, BBP, DIBP) are already regulated by Restrictions or Authorisation[99] under REACH in all uses other than some food contact materials and medical devices (which are subject to ongoing scientific and regulatory evaluation). This reduces the likelihood of identifying exposures over the threshold.

[97] Grouping of aprotic solvents was not based on similar characteristics but these substances were added as a group at the Commissions' request

[98] The list of chemicals is confidential, but we were unable to access (despite multiple attempts) the supplemental data in Eurostat 2007 at http://circa.europa.eu/Public/irc/dsis/reachbaselinestudy/home

[99] The most recent Applications for Authorisation awaiting a decision were considered by RAC to demonstrate "adequate control", in other words worker exposures were below the threshold for effects. Similarly, the Authorisation for the continued use of DBP is based on "adequate control".

Table B3-2: Groupings for 24 out of the 30 Reprotoxic 1A/1B substances investigated further	
Groups	**Substances**
Borates	Diboron trioxide (EC No: 215-125-8; CAS 1303-86-2) Disodium tetraborate, anhydrous (EC No: 215-540-4; CAS No: 1303-96-4, 1330-43-4, 12179-04-3) Boric acid (EC No: 233-139-2; CAS No: 10043-35-3) Perboric acid, sodium salt (EC No: 234-390-0; CAS No: 10332-33-9, 11138-47-9, 12040-72-1, 37244-98-77) Disodium octaborane (EC No: 234-5541-0; CAS 12008-41-2, 12280-03-4)
Dodecyl	Phenol, dodecyl-, branched (EC No: 310-154-3; CAS 121158-58-5) Phenol, dodecyl-, sulfurized, carbonates, calcium salts (EC No: 272-233-8; CAS No: 68784-25-8) Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased (EC No: 272-234-3; CAS No: 68784-26-9) Phenol, dodecyl-, sulfurized, calcium salts (EC No: 272-486-4; CAS No: 68855-45-8) Phenol, dodecyl-, branched, sulfurized (EC No: 306-111-5; CAS No: 96152-43-1) Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate) (EC No: 259-048-8; CAS No: 54261-67-5)
Lead compounds	Lead (EC No: 231-100-4; CAS No: 7439-92-1) Lead di(acetate) (EC No 206-104-4; CAS No: 301-04-2, 6080-56-4) Trilead dioxide phosphonate (EC No: 235-252-2; CAS No: 12141-20-7)
Retinol	Retinol (EC No: 200-683-7; CAS No: 68-26-8) Retinyl palmitate (EC No: 201-228-5; CAS No: 79-81-2)
Tin	Dibutyltin dilaurate (EC No: 201-861-7; CAS No: 77-58-7) Dibutyltin dichloride (EC No: 211-670-7; CAS No: 683-18-1) 2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate (CAS No: 239-622-4; EC No: 239-622-4; CAS no: 15571-58-1) Dibutyltin oxide (EC No: 212-449-1; CAS No: 818-08-6) Dibutyltin bis (2-ethylhexanoate) (EC No: 220-481-2; CAS No: 2781-10-4)
Aprotic Solvents[100]	1-methyl-2-pyrrolidone (NMP) (EC No: 212-828-1; CAS No: 872-50-4) N,N-dimethylformamide (DMF) (EC No: 200-679-5; CAS No: 68-12-2) N,N-dimethylacetamide (DMAC) (EC No: 204-826-4; CAS No: 127-19-5) Tetrahydrothiophene 1,1-dioxide (EC No: 204-783-1; CAS No: 126-33-0

B3.5 Potentially relevant sectors and uses

The sectors and operations which may have a potential for worker exposure are listed below by relevant sectors (NACE 1-3 digits). Key sectors which employ the biggest share of workers potentially exposed to reprotoxic substances are highlighted in grey. In identifying these sectors, no determination has been made as to the extent to which exposures may take place and, if so, whether exposure exceeds the relevant thresholds and/or whether the use of the substance is likely to continue into the future[101]; all potentially relevant sectors are listed here. Please refer to Annexes 10-21 for a more detailed overview of the sub-sectors where exposure is likely to exceed the no-effect thresholds and an assessment of sectors where exposure may reduce in the future due to legislative developments.

[100] Aprotic solvents were added at the request of the Commission at the time of the interim report: their selection was not risk-based.

[101] Sectors that may become less relevant or irrelevant in the future (e.g. due to a REACH restriction) are not excluded from this section. Please see Annexes 9-20 for expected legislative developments.

Table B3-3: High-level overview of potentially relevant sectors and uses												
Sector	2-(4-tert-butylbenzyl)pro-pinolaldehyde	2-ethoxyethanol	Aprotic solvents	Borates	BPA	Dinoseb	Dodecyl phenols	ETU	Lead	Organotins (dibutyltin dichloride)	pTBBA	Retinol
A1.1 Agriculture – growing of non-perennial crops								✓				
A1.2 Agriculture – growing of perennial crops								✓				
A1.4 Agriculture: Animal production												✓
A2.1 Silviculture and other forestry activities								✓				
B06: Extraction of crude petroleum			✓									
B06.1 Extraction of crude petroleum and natural gas			✓									
C10 Manufacture of food products				✓								✓
C13 Manufacture of textiles			✓									
C14.1: Manufacture of wearing apparel, except fur apparel			✓									
C15: Manufacture of leather and related product			✓									
C17 Manufacture of paper and paper products					✓							
C18.1 Printing and service activities related to printing		✓										
C20 Manufacture of chemicals and chemical products			✓	✓			✓		✓			
C20.1 Manufacture of basic chemicals, fertilisers and nitrogen compounds, plastics and synthetic rubber in primary forms	✓	✓			✓	✓		✓		✓		✓
C20.2 Manufacture of pesticides and other agrochemical products	✓					✓		✓				
C20.3 Manufacture of paints, varnishes and similar coatings, printing ink and mastics					✓				✓		✓	
C20.4 Manufacture of soaps and detergents, cleaning and polishing preparations, perfumes and toilet preparations	✓	✓										✓
C20.5 Manufacture of explosives									✓			
C21 Manufacture of basic pharmaceutical products and pharmaceutical preparations			✓	✓								✓

Table B3-3: High-level overview of potentially relevant sectors and uses												
Sector	2-(4-tert-butylbenzyl)propionaldehyde	2-ethoxyethanol	Aprotic solvents	Borates	BPA	Dinoseb	Dodecyl phenols	ETU	Lead	Organotins (dibutyltin dichloride)	pTBBA	Retinol
C22 Manufacture of rubber and plastic products			✓				✓				✓	
C22.1 Manufacture of rubber products								✓	✓	✓		
C22.2 Manufacture of plastic products			✓		✓	✓			✓			
C23 Manufacture of other non-metallic mineral products (glass and ceramics				✓								
C23.1 Manufacture of glass and glass products					✓							
C24 Manufacture of basic metals				✓				✓				
C25 Manufacture of fabricated metal products, except machinery and equipment			✓	✓					✓			
C25.9: Manufacture of other fabricated metal products			✓									
C26 Manufacture of computer, electronic and optical products				✓	✓				✓			
C26.1 Manufacture of electronic components and boards		✓										
C26.11 Manufacture of electronic components			✓									
C27 Manufacture of electrical equipment			✓						✓			
C29 Manufacture of motor vehicles, trailers and semi-trailers				✓			✓		✓			
F41 Construction of buildings					✓							
G Wholesale and retail trade; repair of motor vehicles and motorcycles							✓		✓			
M72 Scientific research and development		✓										
Q86 Human health activities					✓							

B3.6 Exposed workforce

The total number of workers identified as being potentially exposed to each substance is given in the table below. It is important to recognise that these numbers include workers that in practice are not exposed or that may be exposed for very short durations or at concentrations below the no-effect thresholds; they are therefore overestimates of the populations that may actually be at risk.

Although there is the potential for overlap, maximal lower bound and upper bound estimates for the numbers potentially exposed are given in the table below (with figures rounded from those presented in Annexes 10-21 to avoid spurious accuracy). These figures therefore must be treated with caution.

Table B3-4: Potentially exposed workforce - conclusions from substance evaluations (rounded)

Substance	Estimate	Total no. of exposed workers	Men	Women of reproductive age
Lead	Central estimate	17,800	17,000	800
	High estimate	43,300	41,500	1,700 (all women)
BPA	Central estimate	1,000*	690	230
Borates	Central estimate	250,000	190,000	60,000
ETU	Central estimate	Not relevant	Not relevant	45,000
pTBBA	Central estimate	110,000	100,000	10,000
2-ethoxyethanol	Low estimate	1,530	1,360	170
	High estimate	1,650	1,450	200
2,4-TBP	Central estimate	22,000	13,000	8000
Dodecyl phenols	Central estimate	337,900	304,100	33,800
Organotins	High estimate	7,390	5,170	1,660
	Low estimate	1,480	1,030	330
	Central estimate	4,430	3,100	990
Retinol	High estimate	6.33m (6.2m in agriculture)	4.07m (4m in agriculture)	1.21m (1.2m in agriculture)
	Low estimate	6.23m (6.2m in agriculture)	4.02m (4m in agriculture)	1.24m (1.2m in agriculture)
	Central estimate	6.28m	4.045m	1.225m
Dinoseb	High estimate	3,300	2,700	500
	Low estimate	1,600	1,400	300
Aprotic solvents	DMAC and DMF	245,450	204,250	41,210
	NMP	339,680	253,780	85,910
Maximum total potentially exposed - low to central estimates and no adjustment for multiple exposures		7,557,430 (or 1,357,430 without workers using retinol in agriculture)	5,106,600 (or 1,106,600 without workers using retinol in agriculture)	1,495,740 (or 295,740 without workers using retinol in agriculture)
Maximum total potentially exposed – central to high estimates and no adjustment for multiple exposures		7,690,670 (or 1,490,670 without workers using retinol in agriculture)	5,186,630 (or 1,186,630 without workers using retinol in agriculture)	1,530,940 (or 330,940 without workers using retinol in agriculture)
Note: *The vast majority at extremely low levels of exposure and have therefore been discounted. Numbers shown are workers in BPA manufacturing plants which could be exposed above any of the thresholds.				

B3.7 Relevant effects and exposure levels

B3.7.1 List of all relevant reproductive effects

The relevant reproductive effects for the 30 shortlisted substances were identified through a review of the epidemiological and toxicological literature, including the CSRs for each substance, SCOEL opinions and RAC opinions (including within Restriction Dossiers). All adverse effects which have a potential for human effects correlation were identified. In identifying the effects, no determination was made as to whether there would be any evidence of exceedance of the relevant threshold for effects.

For some of these effects, however, it was not possible to define an effect in humans that could be translated to be correlated to a welfare effect and hence valued (either in DALYs or in monetary terms using willingness to pay or cost of illness data). For these effects, no thresholds for effects and dose-response relationship (DRR) for exposures were derived. These effects have therefor not been considered further in this impact assessment, and this is a study limitation.

The full list of effects that was identified is given in Annex 6 and then in the individual substance write-ups (Annexes 10-21). Those for which a DRR was developed and that were considered in more detail are listed in Table B3-5 below.

B3.7.2 Exposure routes

Most of the thresholds and DRRs used for estimation of the numbers of cases of reproductive ill health are for inhalation exposure only and there is, therefore, some potential for underestimation of risks for activities which involve a significant dermal uptake. In order to assess the potential for such underestimation, the key occupational exposure routes are listed below. In this respect, the potential for underestimation is limited in the case of lead, BPA and borates, as inhalation is expected to be the most important route of exposure.

Table B3-5: Overview of exposure routes

Substance	Exposure routes
Lead	Analysis carried out on the basis of Blood Lead Levels; all exposure routes have thus been taken into account.
BPA	Clarity-BPA Programme (2018)[102] & Hines et al (2018)[103]: inhalation dominant Heinala et al (2017)[104]: dermal dominant in some plants Where inhalation equivalents of urinary BPA levels can be estimated from available literature, these do not change the conclusions in terms of the industry sectors where impacts are expected to occur
Borates	Skin uptake limited with main route of exposure being through inhalation
ETU	Insufficient data to determine the dominant route, but inhalation assumed for estimation of the number of cases of ill health.
pTBBA	Inhalation and dermal exposures considered in the analysis as the possible routes of exposure

[102] See https://ntp.niehs.nih.gov/results/areas/bpa/index.html

[103] Hines et al (2018): An Evaluation of the Relationship among Urine, Air, and Hand Measures of Exposure to Bisphenol A (BPA) in US Manufacturing Workers, https://academic.oup.com/annweh/advance-article-abstract/doi/10.1093/annweh/wxy042/5037158?redirectedFrom=fulltext

[104] Heinala et al (2017): Assessment of Occupational Exposure to Bisphenol A in Five Different Production Companies in Finland, Annals of Work exposure Health 61:1, abstract available at https://www.ncbi.nlm.nih.gov/pubmed/28395312

Table B3-5: Overview of exposure routes	
Substance	**Exposure routes**
2-ethoxyethanol	Occupational exposure would mainly be through inhalation and the dermal routes of exposure
2,4-TBP	Occupational exposure would mainly be through the dermal routes of exposure with inhalation considered to be of low relevance for occupational exposure.
Dodecyl phenols	For dodecyl phenols in general, occupational exposure is generally quantified/regulated as inhalation exposure not oral exposure, although for some compounds dermal exposure may play a significant role, easily controlled through industrial hygiene control measures such as protective clothing and hand-wear.
Organotins	Insufficient data to determine the dominant route.
Retinol	The main exposure routes: dermal and oral absorption but inhalation also possible
Dinoseb	Occupational exposure to dinoseb can occur from spraying and mixing operations from manufacture and its applications. Exposure could also occur during the transfer of the substance or mixture (charging and discharging) at dedicated facilities. Exposure routes of dinoseb are from dermal contact and inhalation of aerosols. The dominant route of exposure is dermal exposure and the substance is rapidly absorbed through the skin.
Aprotic Solvents	The main exposure routes are dermal and inhalation

B3.7.3 Exposure levels (exposure above thresholds)

Exposure levels are assessed by means of screening out effects that are not expected to arise under any of the scenarios considered in this study (including the theoretical worst-case scenario). The effects for which it is expected that exposure may exceed the threshold under at least one of the scenarios (including the theoretical worst-case scenarios estimated for some of the substances) and which are monetisable are listed below. The actual exposure levels (air, blood or urinary concentrations) are given in substance-specific Annexes.

Table B3-6: Effects with thresholds exceeding exposure under at least one scenario			
Substance	**Effect from literature**	**Threshold (mg/m^3 except Pb which is BLL µg/dL)**	**Effect quantified in DALYs and monetary terms**
Lead	Increased Odds Ratio for spontaneous abortion	5	Spontaneous abortion or still birth
	Increased incidence of stillbirth	>30	
	Increased frequency of preterm births	5 (0.98)	Low birth weight
	Reduced foetus weight at birth	>30	
	Impaired male fertility (fraction of workers affected)	25	Impaired fertility - male
	Reduced number of foetuses/dam	>30	Impaired fertility - female Pre-eclampsia
	Pre-eclampsia (additional incidence)	5	
	IQ loss in children (IQ points lost per child)	5 (1.7)	IQ loss
BPA	Epithelial hyperplasia (Vagina)	4.38	Impaired fertility - female
	Dilatation of lumen in uterus	4.38	
Borates	Decrease in foetal body weight/litter	2.39	Reduced foetal growth

Table B3-6: Effects with thresholds exceeding exposure under at least one scenario			
Substance	**Effect from literature**	**Threshold (mg/m^3 except Pb which is BLL µg/dL)**	**Effect quantified in DALYs and monetary terms**
	Increased % malformed foetuses/litter (skeletal malformation)	10.1	Developmental abnormality
ETU	Decrease in iodine uptake	4.38	Impaired cognitive development per IQ point
pTBBA	Infertility / inability to impregnate	2.8	Impaired fertility - male
2-Ethoxyethanol	Decreased no. of live foetuses	3	Impaired fertility - female
	Increased no. of foetuses with limb malrotation	3	Skeletal effects or abnormalities of the limbs
2,4-TBP	Increase in mean fraction of abnormal sperm	17.5	Impaired fertility- male
Phenol, dodecyl-, branched	Decreased pup body weight-male-PND 7 (F1)	2.62	Low birth weight (although difficult to conclude that this resulted from reprotoxic effects)
	Decreased pup body weight-female-PND 7 (F1) and 21 (F1)	2.62	
Organotins	Increased post-implantation loss per litter	0.67	Spontaneous abortion or still birth
Retinol	No thresholds exceeded under any of the scenarios		
Dinoseb	Foetuses with microphthalmia	2.63	-
Aprotic Solvents	DMAC: Foetal weight	19	Reduced foetal growth
* F1 = first generation Source: Annexes 10-21			

B3.8 Estimation of the thresholds and development of the DRRs

B3.8.1 Summary of the approach

This section summarises the approach to the development of the DRRs. The specific steps involved in the estimation of the no-effect thresholds and derivation of the DRRs are set out in more detail in Annex 1.

For each of the compounds prioritised for more detailed assessment, a literature search was conducted to identify relevant papers and reports (including the REACH Registration and C&LI databases), presenting data/findings of relevance to characterisation of the potential reproductive toxicity of that compound. Data sources relating to both human and experimental investigations were considered.

In some cases, it was possible to consider groups of closely related compounds showing common patterns of biological activity, thus simplifying the subsequent estimation of the burden of effects. As described elsewhere in this report, the focus when reviewing the toxicological (animal) and, in some instances, (human) clinical evidence was on identifying reported changes that attained a level of statistical significance ($p>0.05$) and showed consistent evidence of dose-response. Hence, potentially spurious differences from controls that were noted for low or intermediate dosages, in the absence of a corresponding effect at higher dosages, were omitted from further consideration. Statistically

significant trends where individual data points never rose to statistical significance, were also considered.

Consequently, from each information source, the effect (i.e. each finding of potential toxicological relevance) that met these criteria was identified. For each effect we then calculated the 'threshold of effect' (ToE). Generally, the ToE was considered to be the NOAEL as identified in the data source for that effect/endpoint; if no NOAEL was identified, i.e. the LOAEL was the lowest dose, the LOAEL for the endpoint was identified and the assumption made that the ToE was the LOAEL/10. The experimentally-derived ToE was further adjusted to give a **human equivalent exposure** value using standard default assumption factors (from ECHA, 2012 and SCOEL, 2017) for allometric scaling based upon the average weight of a human; the duration of exposure on an average working day; and the exposure route. With regard to exposure route, for most compounds/compound groups adjustments were made assuming that the main human occupation route was inhalation; i.e. all data was expressed in inhalation mg/m3 equivalents regardless of original route or units of exposure. In the case of lead (Pb), exposure was evaluated not through direct exposure measurements but in terms of blood Pb to better reflect available (historic and retrospective) human exposure data.

Importantly, as the objective of the current exercise is **solely** to assess the potential health burden and socioeconomic consequences of occupational exposure (i.e. the welfare effects), it is important to note that several of the adjustment factors routinely applied during chemical risk assessments that are intended to establish occupational exposure limits (e.g. DNELs or OELs) were omitted. The adjustment factors omitted include those relating to: intra- and inter-species variability; duration of study (correction was made for the length of daily inhalation exposure); nature of effect being considered; robustness of individual studies and numbers of studies available in the database.

Wherever possible for each effect endpoint identified, a linear dose-response function was derived. This linear relationship was established at the lowest point of the dose equation (the NOAEL or x intercept) and extended to LOAEL. This linear dose response relationship was represented as a "slope" value, with lower and upper limits, using the methodology described in Annex 1. Depending on the actual slope of the dose response curve (which is unlikely to be exactly linear), a linear dose-response relationship can be over or underestimating the actual slope of the relationship. For most chemicals, studies included at best 3 or 4 dosages which means that even when the NOAEL determined is either the lowest or second lowest dosage, one only has 2 to 3 points on a curve, requiring large parts of the curve to be mathematically estimated. Hence, the most practical approach is to assume a linear dose-response between LOAEL and NOAEL. Only in the case of a statistically significant trend would one have the opportunity to fit multiple dosages on a "curve". A measure of quality control is that in many cases, but not all, our Threshold equalled the DNEL multiplied by the assessment factors. In other words, our conclusion regarding the most sensitive effect matched that of more extensive studies. Thus, we concluded that a linear dose-response would provide adequate precision for the current study.

Wherever considered toxicologically practicable and relevant (in terms of reflecting an identifiable effect in humans), individual dose-response functions were then used to provide estimates of the "magnitude of effect" that might occur at various levels of human exposure. However, in many cases, the metrics identified during the review of toxicological evidence were judged unsuitable for such an extrapolation exercise. For example, it is not possible to 'translate' an estimate of a percentage increase in mean testis weight at a particular dosage in a toxicity study into a meaningful estimate of how many workers might experience testicular changes leading to male infertility in a worker population. Similarly, a 4% decrease in sperm count at a given dosage would have no reproductive adverse consequences for the vast majority of an occupational group of male workers although such a decrease in sperm count might be sufficient to result in a small number of male workers with pre-

existing low sperm count (i.e. at the clinical border line between being naturally fertile and infertile) becoming clinically infertile and therefore needing medical intervention to successfully reproduce. In other cases, however, it was possible to model potential effects using a categorisation approach (e.g. to estimate an increase in 'low birth weight' instances) or to derive estimates of the percentage of the human population that might be affected as a result of a given level of exposure.

B3.8.2 Implications of non-inclusion of assessment factors

There are significant implications of the approach adopted here. The omission of adjustment factors relating to intra- and inter-species variability; duration of study; and nature of effect being considered, could result in the burden of effects being underestimated (i.e. the resulting assumed threshold may be significantly higher than if these factors were applied). In contrast, inclusion of REACH assessment factors specifically aimed at addressing possible uncertainties arising from the numbers of studies available, for example, could result in the true effects from exposures to reprotoxins being over-estimated. This latter issue is also one which distinguishes between the approach taken by SCOEL in setting Occupational Exposure Limit values, which does not rely on the automatic use of pre-defined assessment factors, and the REACH risk assessment approach.

It is important to note that due to the application of assessment factors, most (and possibly all) of the REACH DNELs communicated by registrants to their downstream supply chain are well below the NOAEL or OEL where one exists. As a result, if the risk management measures identified in REACH eSDS are sufficient to ensure exposures would not exceed the Registration DNEL and these measures are applied by downstream users, then the burden of health effects from current occupational exposures should be minimised.

In some cases, however, Registration DNELs are significantly below the levels set by national OELs (often, not surprisingly, by the magnitude of the assessment factors). This raises the question as to whether one should assume for this assessment that downstream users adhere to the national OEL or to the DNEL communicated to them in the exposure assessment. As indicated above, for the purposes of this assessment, we have assumed that the OEL is given priority by both employers and national authorities when carrying out enforcement.

B3.9 Bottom-up estimates of cases of ill health

B3.9.1 Introduction to the scenarios

There are large differences between the substances in terms of the data available and whether there is any indication of exceedance of the thresholds for reprotoxic effects. Generally speaking, the study team attempted to model the following three scenarios for each substance:

- **Scenario A (Measured data):** Worker exposure at measured exposure concentrations identified through literature review and/or consultation for this study. Where sufficient data are available, a reasonable worst-case scenario was preferred, reflecting the fact that exposure at certain stages of pregnancy may in some cases be sufficient for the development of reprotoxic effects. It is important to note that measured exposure data reported by companies can entail a positive bias due to self-selection;

- **Scenario B (OELs):** Exposure at the respective national OEL or a weighted average of national OELs; and

- **Scenario C (Theoretical worst case):** Theoretical worst-case scenario, whereby workers are exposed at higher national OEL or either 10x or 100x DNEL. This reflects uncertainty about the degree to which companies are successful in reducing exposures to the level of REACH DNELs.

The criteria determining whether the theoretical worst-case scenario is based on 10x or 100x DNEL included: a) are strict exposure controls likely to be in place or are there any open processes? And b) what is the level required for at least one of the thresholds to be exceeded?

Not all scenarios have been estimated for every substance. For example, where comprehensive measurement data are available and a worst-case scenario would be clearly unrealistic, it was not estimated. A summary of the scenarios that have been estimated for each substance is provided together with the estimated numbers of cases of reproductive ill health below. More detailed reporting is given in the Annexes.

B3.9.2 Estimated total burden for the shortlisted chemicals

The total number of cases per annum for each of the 12 substance groups by scenario are given in Table B3-7 below. In total, between 19 and 1,041 cases were estimated across the range of health effects considered, and for which exposures exceeded thresholds for effects under at least one of the scenarios.

The estimated numbers of cases by substance and ill health effect are then summarised in Table B3-8 for all cases where exposures were predicted as being above the threshold for effects under at least one of the scenarios. Note that this was only the case for substances/substance groups.

Table B3-7: Total number of cases per annum estimated under each of the scenarios for shortlisted substances/substance groups (rounded)

Substance	Sc 1A: Measured (L1 for Pb)	Sc 1B: Measured (L2 for Pb)	Sc 2: OELs (L3 for Pb)	Sc 3: theoretical worst case (L3 for Pb)
Lead	15.9	119.6	129.5	129.5
BPA	8	8	41	41
Borates	0	0	0	137.6
ETU	0	0	0	1013
pTBBA	0	0	0	69
2-Ethoxyethanol	N/A	N/A	0.10	0.32
2,4-TBP	0	0	N/A	17
Dodecyl-phenol, branched	N/A	N/A	N/A	N/A
Organotins	N/A	N/A	0	11.6
Retinol	N/A	N/A	N/A	N/A
Dinoseb	N/A	N/A	0	0.7
Aprotic solvent - DMAC	0	0	9.7	9.7
Aprotic solvent – DMF	N/A	N/A	N/A	N/A
Total	**24**	**128**	**180**	**1,429**

Table B3-8: Total number of cases per annum by monetisable effect for 12 shortlisted substance groups (rounded)						
Effect	**Substances**	**Potentially exposed workforce***	**Sc 1A: Measured (L1 for Pb)**	**Sc 1B: Measured (L2 for Pb)**	**Sc 2: OELs (L3 for Pb)**	**Sc 3: worst case (L3 for Pb)**
Spontaneous abortion or stillbirth	Lead	(17,800 – 43,300)	2.5	14	7.3	7.3[a]
	Organotins	4,400	N/A	N/A	0	11.6[b]
	2-ethoxyethanol	(1,500 – 1,650)	N/A	N/A	0.08	0.25[c]
	TOTAL	-	**2.5**	**14**	**7.38**	**19.2**
Impaired fertility - male	Lead	(17,800 – 43,300)	0	95	115	115[a]
	pTBBA	110,000	0	0	0	69[b]
	2,4-TBP	22,000	0	0	N/A	17[b]
	TOTAL	-	**0**	**95**	**115**	**201**
Impaired fertility - female	Lead	(17,800 – 43,300)	0	1.6	0	0[a]
	BPA	600,000	8	8	41	41[d]
	TOTAL	-	**8**	**9.6**	**41**	**41**
Low birth weight - normal to low	Lead	(17,800 – 43,300)	0.755	0.566	0.566	0.57[a]
	Borates	250,000	0	0	0	123.95[e]
	Aprotic solvent - DMAC	245,500	0	0	9.17	9.17[d]
	TOTAL	-	**0.76**	**0.57**	**9.74**	**133.69**
Low birth weight - low to very low	Lead	(17,800 – 43,300)	0.035	0.026	0.026	0.026[a]
	Borates	250,000	0	0	0	5.75[e]
	Aprotic solvent - DMAC	245,500	0	0	0.42	0.42[d]
	TOTAL	-	**0.035**	**0.026**	**0.45**	**6.20**
Low birth weight - very low to extremely low	Lead	(17,800 – 43,300)	0.010	0.008	0.008	0.008[a]
	Borates	250,000	0	0	0	1.85[e]
	Aprotic solvent - DMAC	245,500	0	0	0.12	0.12[d]
	TOTAL	-	**0.010**	**0.008**	**0.13**	**1.98**
Skeletal effects or abnormalities of the limbs	Borates	250,000	0	0	0	6.05[e]
	2-Ethoxyethanol	(1,500 – 1,650)	N/A	N/A	0.022	0.069[c]
	TOTAL	-	**0.000**	**0.000**	**0.022**	**6.12**
Impaired cognitive development 2 IQ points	ETU	N/A	0	0	0	1013[b]

Table B3-8: Total number of cases per annum by monetisable effect for 12 shortlisted substance groups (rounded)						
Effect	**Substances**	**Potentially exposed workforce***	**Sc 1A: Measured (L1 for Pb)**	**Sc 1B: Measured (L2 for Pb)**	**Sc 2: OELs (L3 for Pb)**	**Sc 3: worst case (L3 for Pb)**
Number of children affected by IQ loss	Lead	(17,800 – 43,300)	12	7.7	5.7	5.7[a]
Total number of IQ points lost			3.3	7.5	8	8[a]
	TOTAL IQ POINTS		**3.3**	**7.5**	**8**	**2034**
Foetuses with microphthalmia	Dinoseb	1,600 – 3,300)	N/A	N/A	0	0.69[b]
Pre-eclampsia	Lead	(17,800 – 43,300)	0.6	0.7	0.9	0.9[a]
Notes: *Worst case scenarios: [a]L3 for Pb; [b]100X DNEL; [c]Highest defined MS OEL; [d]Scenario 2 OEL; [e]10X DNEL* ** Since there is a potential for overlap, no totals across all substances are provided. Data in brackets are ranges.*						

B3.9.3 Extrapolation to other reprotoxic substances

The above analysis has only covered the short-listed substances. In order to reflect the potential number of cases associated with Reprotoxic 1A/1B substances not covered by this analysis, extrapolation from the substances/substance groups evaluated in detail is required (i.e. from the 30 substances / 6 groups to other Reprotoxic 1A/1B substances).

The risk ranking methodology used for prioritisation and shortlisting of the 30 substances was carried out on the basis of geometric means of the relevant tonnage bands and DNEL (see Section B4 and Annex 1). As a conservative approach, this method has been slightly modified for the purposes of the extrapolation, with the implied tonnages that reflect the number of active registrations taken as the basis for calculations. This approach assigns a slightly lower share of the overall risk ranking score for the original 12 shortlisted substances/substance groups. As described earlier and in Annex 9, the risk ranking score for the original 27 chemicals accounted for around 97% of all "risk" from the set of Reprotoxic 1A/1B substances which are not also carcinogenic or mutagenic 1A/1B substances (C/M 1A/1B); it increased marginally to an estimated 98% with the addition of the three aprotic substances.

The extrapolated results are given below. Please note that the estimates given below for 'R 1A/1B and C/M 1A/1B' and R2 substances should not be treated as precise estimates but are merely illustrative of the fact that these substances could potentially account for a significant proportion of the overall burden of reproductive ill health.

Table B3-9: Total number of cases per annum estimated under each of the scenarios for 30 substances		
Substances	**Risk characterisation factor**	**Cases per annum***
30 substances (12 substances/groups)	7	24-180 (1,429)
All 'R 1A/1B but not C/M 1A/1B'	8	27-206 (1,633)
R 1A/1B and C/M 1A/1B	49 but not quantified**	0**
R2	63	215-1,623 (12,859)
Notes: *Range: Scenarios 1 and 2, value in brackets is for the theoretical worst-case scenario		

Table B3-9: Total number of cases per annum estimated under each of the scenarios for 30 substances		
Substances	**Risk characterisation factor**	**Cases per annum***
**Not quantified since, generally speaking, the R "risks" of CMR are underwhelmed by the CM effects because the lack of or lower thresholds and /or fairly steep slopes for CM classified chemicals. One can thus assume that classifying chemical as CM is "protective" of its reproductive effects, always assuming of course that one meets the CM control requirements.		

Key uncertainties

It is possible that there are several data gaps in the estimates of reprotoxic effects presented above. Table B3-10 summarises the key data gaps and their potential impact on the bottom-up estimates in particular. Taken together, these suggest that the bottom up estimates could be underestimates.

Table B3-10: Uncertainty (data gap) – magnitude of uncertainty	
Type of uncertainty	**Magnitude of uncertainty**
Reprotoxic effects without quantitative effects calculations	Moderate
Reprotoxic effects that could not be monetised i.e. no welfare effect could be assigned to the effect per se	Moderate to high
Only reprotoxins that are not C and M are covered in this report	Low
Not all reprotoxins that are not C and M are covered in this report	Low
Non-reprotoxic effects from reprotoxins were not addressed	Moderate
Self-classified reprotoxins were not all taken into account	Moderate

Our methodologies used for identifying chemicals and calculating thresholds and slopes are all considered to be skewed "conservatively" i.e. tend to overestimate. This inherent overestimation leads us to believe our economic impacts estimates may also be conservative i.e. tend to overestimate the actual effects. With respect to effects that are not quantified, the assessment of the level of uncertainty this leads to is based on:

- Most missing slopes were at thresholds more than one order of magnitude above the lowest threshold, i.e. the could be ignored; and
- Most missing data was for minor effects.

Only a few endpoints were selected for inclusion in the risk calculations. These endpoints needed to meet very specific qualifications:

- Effects had to be at the lowest (or very nearby the) threshold available for that chemical, e.g. an endpoint was ignored if its threshold was an order of magnitude or more above the lowest threshold;
- Similarly, endpoints were ignored if their slopes were more than an order of magnitude smaller than the highest slopes at a similar threshold;
- Some endpoints (mostly from animal studies) could not be monetized due to: the human equivalent effect having no clearly identifiable DALY associated with it (e.g. a decrease in thyroxine levels); or the animal effect having no human equivalent (e.g. an increase in supernumerary ribs).

The first two factors are expected to impose at worst a 10% underestimate, while the latter factor is much more uncertain and leads to greater uncertainty even if most of these effects are obscure (but not necessarily negligible).

As noted previously, reprotoxins are generally not classified as just reprotoxic. In this report, we have focused on the chemicals classified as reprotoxic and not also carcinogenic or mutagenic. Generally speaking, the reprotoxic "risks" of CMRs are overwhelmed by the carcinogenic and mutagenic effects,

simply because the lack of or lower thresholds and /or fairly steep slopes for carcinogenic and mutagenic classified chemicals[105]. One can thus assume that classifying a chemical as carcinogenic and mutagenic is "protective" of its reproductive effects, always assuming of course that one meets the carcinogenic and mutagenic risk guidelines.

For most sensitisers (but not all), effects occur at much lower thresholds (for the most sensitive individuals) than the reprotoxin thresholds. Similarly, for other effects a similar mixed effect can be observed. Some reprotoxins have higher chronic systemic toxicity than reproductive toxicity, others the reverse. It is therefore

The shortlisted substances/substance groups focus exclusively on reprotoxins not carcinogens or mutagens. A risk screening approach was used to select the 30 chemicals in the original dataset for assessment. Not covering all Reprotoxic 1A/1B substances is an obvious source of uncertainty.

Furthermore, based on the number of self-classifications available, there are numerous chemicals that may eventually formally receive a harmonised classification. How many of these would also be classified for carcinogenicity and mutagenicity is unknown. The fact that they have not yet received harmonised classifications tends to indicate that the chemicals are not highly potent and some may eventually be classified R2. In addition, they tend to be the smaller volume chemicals.

[105] Admittedly this is a generalization, but it is hard to come up with a reverse example.

B4 Valuation of the Burden of Ill Health and Potential Future Changes Relevant to the Baseline

B4.1 Introduction

This estimated numbers of cases of different reprotoxic effects from both the bottom up and top down analyses have been valued in monetary terms as part of setting the policy baseline. The results of this exercise are presented here together with a review of potential future changes to the baseline and which may impact on the burden of ill health in the future.

Key findings

The economic costs of the bottom up calculations for the health burden from workplace exposures to Reprotoxin 1A and 1B substances are estimated at between (rounded):

- €460,100 for the 30 substances and €525,850 after extrapolation under Scenario 1a; and
- €38.4 million for the 30 substances and €43.9 million after extrapolation under Scenario 3 (unrealistic worst-case scenario).

The estimates under the top-down analysis are higher, given the higher number of cases predicted through this method. Based on the use of willingness to pay values, these are estimated at a between €9.1 and €24.3 million per annum for the geometric mean for developmental effects and between €29.7 and €79.5 million per annum for fertility and maternal effects for the geometric mean. At the maximum worst case (Scenario 1 which includes welding and taking the worst-case scenario), the figures rise to €91 million for developmental effects and €290 million for fertility and maternal effects.

Although the numbers of cases calculated under the two approaches are relatively low, the 30 substances are expected to account for around 97% of risk. In addition, the top down assessment has a multiplier of 2 built into the estimates to try and account for potential worker exposures above the threshold for effects to other Reprotoxic 1A/1B substances that are not also Carcinogens or Mutagens 1A/1B. In this respect, it is important to remember that the starting point for the assessment was a review of the Classification and Labelling Inventory, which found that there were only 52 fully registered or intermediate substances with harmonised classifications as Reprotoxic 1A/1B substances that were not already Restricted or subject to Authorisation, or held classifications as Carcinogens 1A/1B and, thus, would fall under the CMD for OSH purposes.

A range of drivers are likely to reduce exposures to Reprotoxic 1A/1B substances into the future, not least regulatory pressures on such substances from REACH Authorisation and to a lesser degree Restrictions. This includes increasing levels of worker protection through, e.g. collective worker protection measures and other actions taken by employers under the CAD, as well as substitution to substances of lower toxicity, whether voluntarily or due to regulatory pressures. In particular, for key substances such as lead, action is being taken by the relevant sectors to reduce worker exposures with this coming on top of decreases in the number of exposed workers. Furthermore, the potential benefits of a lower binding BLV for lead under the CAD is recognised by the industry as well as by authorities. This includes borates, 2-ethoxyethanol, organotins, DMF and Dimethyl formamide, NMP and DMAC.

Regulatory pressures also stem from ongoing actions at the Member State level under OSH legislation with respect to the revision or introduction of national OELs for reprotoxic substances.

Such actions may be reinforced by REACH, with reprotoxic substances already subject to REACH Restrictions or Authorisation, or being placed on the Candidate List.

Key limitations

Valuation of impacts has drawn on the use of DALYs avoided and direct and indirect cost of illness estimates for the bottom up approach and willingness to pay estimates for the top down approach. It did not prove possible to apply the DALYs approach to the top down estimates due to the number and range of developmental effects that would require consideration. The combined use of the two approaches should ensure that the end estimates are indicative of the range of health impacts. However, both approaches yield only indicative values of the benefits. The DALY estimates are not specific to each substance but have been developed to be indicative of the impacts of different types of ill-health. Good data on years of life lost are not available in all cases, potentially impacting on the reliability of the estimates. In addition, the study team had to match willingness to pay values developed for ECHA to different types of health effects. The fact that these valuations are not specific leads to uncertainty.

Finally, it has only been possible to estimate the potential cases of reprotoxic effects that are currently associated with workplace exposures. Exposures to reprotoxic chemicals at levels below the threshold for reprotoxic effects may lead to other health effects not considered here. Where this is the case, there will be an additional burden of ill health not captured by this study.

B4.2 Valuation for the bottom up approach and top down approaches

B4.2.1 Results for the bottom up approach

The valuation methodology set out in Annex 1 to this report was applied in order to place a monetary value on the calculated baseline health burden for workers exposed to reprotoxins. Two different approaches to the valuation were applied:

- Valuation based on DALYs avoided; and
- Valuation based on the direct and indirect costs of illness.

Valuation based on DALYs avoided

Table B4-1 provides the estimated monetary value per case of health effects based on a DALY being valued at €100,000. These figures are given in present value terms, as they take into account the age at which life years would be lost for those specific effects where this is expected. Only those health effects relevant to this analysis are presented.

Valuation based on cost-of-illness

Cost of illness data were sourced through literature searches of Medline and Google and through health care service provider registries. European data was favoured and corroborated by other supporting data, where possible. These are, however, rough estimates of costs, as costs between member states can vary widely. The results are presented in Table B4-2.

Overall cost of ill health due to exposure

Based on the costs presented in Table B4-3 and the number of cases of ill health derived for each substance analysed in this report, an estimate for the total cost (direct, indirect and intangible) can be calculated. This is given in Table B4-3 below.

Table B4-1: Bottom-up estimates of the economic value of the burden of ill health (€)				
	SC1a	Sc1b	Sc2	Sc3
Total cost fertility related cases	378,180	1,326,070	1,737,470	2,559,140
Total cost developmental cases	20,270	15,200	286,710	10,753,780
Total cost cognitive development	31,680	72,000	76,800	19,526,400
Total – Bottom-up	**460,110**	**1,435,760**	**2,487,870**	**38,382,750**
Total after extrapolation	**525,840**	**1,640,870**	**2,843,280**	**43,866,000**

B4.2.2 Results for the top down approach

It was not possible for the study team to make linkages between the different types of congenital anomalies covered by the Eurocat database and DALYs (or indeed cost of illness estimates). As a result, we have used willingness to pay values developed for ECHA specific to chemical exposures and the types of effects associated with exposures to Reprotoxic 1A/1B substances.

The willingness to pay values used for these purposes as well as the resulting estimates are given in Tables B4-4 and B4-5 for fertility and developmental effects respectively, and for both top down scenarios and the geometric mean of the two scenarios.

Table B4-2: Present value of expected (severity weighted) number of DALYs per case (discounted @4%, years 1 to 80)									
Health effect	**Individual impacted and link to exposures**		**Severity frequency**	**DALYs**			**Present value of DALYs lost (Euro, 2016)**		
	Worker or offspring	**Effect passed by Male/ Female**	**% by severity (mild, mod, severe)**	**Disability weights (DW)**	**Years lived with disability (L)**	**Years life lost (YLL)**	**Total discounted DALYs per severity case**	**Weighted, discounted DALYs per case**	**Present value Expected/average DALYs per case**
Impaired or reduced fertility female	Worker	F	100%	0.008	1	0	0.008	0.008	800
Impaired fertility - male	Worker	M	100%	0.008	1	0	0.008	0.008	800
Spontaneous abortion	Worker	F	100%	0.114	1	0	0.114	0.114	11,400
Still birth	Worker	F	100%	0.114	5	0	0.528	0.528	52,800
Low birth weight: normal–low	Offspring	F	100%	0.011	80	0	0.257	0.257	25,734
Low birth weight: low–very low			100%	0.185	70	10	4.849	4.849	484,886
Low birth weight: very low–extremely low			100%	0.421	40	40	12.455	12.455	1,245,538
Impaired cognitive development – per IQ point	Offspring	F	-	-	-	-	-	-	9,600
Skeletal effects or abnormalities of the limbs	Offspring	F	40%	0.028	80	0	0.670	6.425	642,477
			40%	0.317	80	0	7.581		
			20%	0.581	40	40	15.622		
Pre-eclampsia	Worker	F	100%	0.324	1	0	0.324	0.324	465,199
	Offspring	F	100%	0.185	70	10	4.328	4.328	
https://ecdc.europa.eu/sites/portal/files/documents/Haagsma-PopHealthMetrics-2014-Disability-weights.pdf *https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(15)00069-8/fulltext*									

Table B4-3: Indirect and direct cost-of-illness data for all relevant endpoints					
Description	**Direct/ Indirect cost**	**Cost per case (€)**	**Proportion by severity**	**Weighted cost per case (€)**	**TOTAL cost per case (€)**
Infertility – male or female					
Cost, per treated couple, of medically assisted reproductive treatment (irrespective of whether terminated by live birth)[a]	Direct	6,607	1	6,607	7,005
Productivity losses (15.6 days over 18 months) adjusted to 1 year – 2 people[b]	Indirect	398	1	398	
Spontaneous abortion					
Medical cost of spontaneous abortion without intervention[c]	Direct	693	0.971	673	734
Medical cost of spontaneous abortion with intervention[c]	Direct	2,105	0.029	62	
Still birth					
Medical costs of still birth, including investigations into cause of death[d]	Direct	2,223	1	2,223	6,691
Additional direct cost of care in subsequent pregnancies after still birth – high estimate[d]	Direct	1,978	1	1,978	
Productivity losses – year 1 – 50% normal work[d]	Indirect	2,490	1	2,490	
Low birth weight					
Paediatric Faltering Growth (Failure to Thrive) with CC Score 0[c]	Direct	1,112	1	1,112	1,112
Paediatric Faltering Growth (Failure to Thrive) with CC Score 1[c]	Direct	1,438	1	1,438	1,438
Cost of VLBW babies for first 18 months of life (Societal - direct (above))[e]	Direct & Indirect	30,230	1	30,230	30,230
Skeletal effects/abnormalities of limbs					
Total life-time costs for patients with spina bifida (inc. indirect costs and increased morbidity[f]	Direct & indirect	528,425	1	528,425	528,425
Pre-eclampsia					
Mean cost per woman of pre-eclampsia with expectant management (Euros, 2007). This includes direct medical costs, indirect costs to patients (travel and informal care), and productivity loss[g]	Direct & indirect	7,908	1	7,908	7,908
Impaired cognitive development					
Impaired cognitive development – per IQ point	Direct & indirect	9,600	1	9,600	9,600

[a]Christiansen *et al.* (2014) *Acta Obs Gyn Scand* 93;64–72; [b]Wu A *et al.* (2013) *Fertility and Sterility* 99;2025–30; [c]*NHS Reference costs (2017)* https://improvement.nhs.uk/resources/reference-costs/; [d]Heazzell *et al.* (2016) *Lancet* 387;604–16; [e]Cavallo M *et al.* (2015) *Italian J Paediatrics* 41;59; [f]Yi Y *et al.* (2011) *Eur J Paediatr;* 170;1391–400; [g]VIjgen SMC *et al.* (2010) *BJOG* 117;1577–85.

Most of the valuations included in the above table are based on stated preferences surveys undertaken for ECHA with the explicit aim of deriving economic valuations for use in the context of REACH Restrictions and Authorisation. The original study reports can be found on ECHA's website[106]. Because of concerns over how to interpret some of the study results, a critical review carried out by Dubourg for ECHA (2016)[107]. This review recommended the use of the lower bound values (€21,600 for the value of a statistical pregnancy, €4,300 for a minor birth defect, €128,200 for a major internal birth defect, €25,700 for a major external birth defect, and €126,200 for very low birth weight) due to concerns over the validity of the upper bound values which reflect public good values and are

B4.2.3 Results for the top down approach

It was not possible for the study team to make linkages between the different types of congenital anomalies covered by the Eurocat database and DALYs (or indeed cost of illness estimates). As a result, we have used willingness to pay values developed for ECHA specific to chemical exposures and the types of effects associated with exposures to Reprotoxic 1A/1B substances.

The willingness to pay values used for these purposes as well as the resulting estimates are given in Tables B4-4 and B4-5 for fertility and developmental effects respectively, and for both top down scenarios and the geometric mean of the two scenarios.

Most of the valuations included in the above table are based on stated preferences surveys undertaken for ECHA with the explicit aim of deriving economic valuations for use in the context of REACH Restrictions and Authorisation. The original study reports can be found on ECHA's website[108]. Because of concerns over how to interpret some of the study results, a critical review carried out by Dubourg for ECHA (2016)[109]. This review recommended the use of the lower bound values (€21,600 for the value of a statistical pregnancy, €4,300 for a minor birth defect, €128,200 for a major internal birth defect, €25,700 for a major external birth defect, and €126,200 for very low birth weight) due to concerns over the validity of the upper bound values which reflect public good values and are considered to be impacted by the nature of the valuation scenario and other aspects of questionnaire design. In line with these recommendations, we have adopted the lower bound estimates for the purposes of this study, and adjusted them for 2018 prices.

However, for some endpoints the choice of valuation has been conservative, with this particularly being the case for ectopic pregnancies, placenta previa and abruptio placentae. For all of these, we have assumed a worst-case outcome of loss of the foetus, leading to a clear overestimate of the health impacts.

[106] https://echa.europa.eu/support/socio-economic-analysis-in-reach/willingness-to-pay-to-avoid-certain-health-impacts

[107] ECHA (2016): Valuing selected health impacts of chemicals: Summary of the Results and a Critical Review of the ECHA study, February.

[108] https://echa.europa.eu/support/socio-economic-analysis-in-reach/willingness-to-pay-to-avoid-certain-health-impacts

[109] ECHA (2016): Valuing selected health impacts of chemicals: Summary of the Results and a Critical Review of the ECHA study, February.

Table B4-4: Estimated economic value of fertility related burden of ill health due to workplace exposures to Reprotoxic 1A/1B substances				
	Willingness to pay value per case	Estimates based on geometric mean of worst and best case	Best case (excludes all missing values from the Sumer data)	Worst case (includes all missing values from the Sumer data at threshold for reporting as not significant – where NS <40)
Scenario 1				
Secondary female infertility	23,500	1,044,400	261,100	3,916,500
Ectopic pregnancy	4,900,000	41,215,600	10,303,900	154,558,500
Placenta previa	4,900,000	9,623,900	2,406,000	36,089,800
Abruptio placentae	4,900,000	12,553,000	3,138,200	47,073,700
Endometriosis	23,500	7,700	1,900	28,900
Spontaneous abortion and miscarriages	46,000	2,592,600	648,100	9,722,200
Still births	4,900,000	6,485,700	1,621,400	24,321,400
Male infertility	23,500	5,929,700	2,391,000	14,633,000
Totals		79,452,600	20,771,700	290,343,900
Scenario 2				
Secondary female infertility	23,500	391,600	130,500	2,349,900
Ectopic pregnancy	4,900,000	15,455,900	5,152,000	92,735,100
Placenta previa	4,900,000	3,609,000	1,203,000	21,653,900
Abruptio placentae	4,900,000	4,707,400	1,569,100	28,244,200
Endometriosis	23,500	2,900	1,000	17,400
Spontaneous abortion and miscarriages	46,000	972,200	324,100	5,833,300
Still births	4,900,000	2,432,100	810,700	14,592,800
Male infertility	23,500	2,104,100	573,800	7,459,900
Totals		29,675,200	9,764,200	172,886,500

Table B4-5: Estimated economic value of developmental effects due to workplace exposures to Reprotoxic 1A/1B substances				
	Willingness to pay value per case	Estimates based on geometric mean of worst and best case	Best case (excludes all missing values from the Sumer data)	Worst case (includes all missing values from the Sumer data at threshold for reporting as not significant – where NS <40)
Scenario 1				
Late neoanatal death (day 7-27)	4,900,000	1,326,200	331,600	4,973,400
Perinatal death	4,900,000	8,825,300	2,206,300	33,094,800
Infant death	4,900,000	7,231,600	1,807,900	27,118,500
Preterm birth (<32 weeks)	134,000	53,900	13,500	202,100
Preterm birth (32-36 weeks)	134,000	315,800	78,900	1,184,100
Low birth weight (<1,500g)	134,000	51,200	12,800	192,000
Low birth weight (<2,500g)	134,000	347,300	86,800	1,302,400
Small for gestational age	134,000	4,975,200	1,243,800	18,656,800
Neutral tube effects	134,000	46,400	11,600	173,900
Anencephalus and similar	134,000	18,600	4,600	69,600
Spina bifridda	134,000	22,800	5,700	85,400
Hydrocephaly	134,000	22,100	5,500	82,800
Eye defect	46,000	5,200	1,300	19,300
Congenital heart defect	136200	330,500	82,600	1,239,400
Severe congenital heart defect	136,200	94,300	23,600	353,700
d-transposition great arteries	136,200	12,100	3,000	45,500
Ventiscular septal defects	136,200	164,200	41,000	615,700
Atrial septal defects	136,200	69,300	17,300	260,000
Atrioventicular septal defects	136,200	10,300	2,600	38,500
Tetralogy of Fallot	136,200	14,100	3,500	52,900
Hypoplastic left heart S.	136,200	12,200	3,000	45,700
Patent ductus arteriosus	136,200	20,700	5,200	77,700
Coarctation of aorta	136,200	17,900	4,500	66,900

Table B4-5: Estimated economic value of developmental effects due to workplace exposures to Reprotoxic 1A/1B substances				
	Willingness to pay value per case	Estimates based on geometric mean of worst and best case	Best case (excludes all missing values from the Sumer data)	Worst case (includes all missing values from the Sumer data at threshold for reporting as not significant – where NS <40)
Outflow tract defects	136,200	80,400	20,100	301,500
Conotruncal defects	136,200	37,400	9,400	140,300
Cleft palate	27,700	5,200	1,300	19,500
Cleft lip, w/out palate	27,700	7,800	2,000	29,300
Anorectal atresia and stenosis	136,200	14,400	3,600	53,900
Cryptorchidism	36,700	103,600	25,900	388,300
Hypospadias	21,600	13,900	3,500	52,200
Testicular cancer	136,200	2,500	600	9,500
Clubfoot-Talipes equinovarous	27,700	10,600	2,600	39,700
Limb deficiency (defects)	27,700	4,600	1,200	17,300
Craniosynostosis	136,200	11,600	2,900	43,400
Gastroschisis	136,200	12,800	3,200	48,200
Totals		24,291,900	6,073,000	91,094,500
Scenario 2				
Late neoanatal death (day 7-27)	4,900,000	497,300	165,800	2,984,100
Perinatal death	4,900,000	3,309,500	1,103,200	19,856,900
Infant death	4,900,000	2,711,900	904,000	16,271,100
Preterm birth (<32 weeks)	134,000	20,200	6,700	121,200
Preterm birth (32-36 weeks)	134,000	118,400	39,500	710,500
Low birth weight (<1,500g)	134,000	19,200	6,400	115,200
Low birth weight (<2,500g)	134,000	130,200	43,400	781,500
Small for gestational age	134,000	1,865,700	621,900	11,194,100
Neutral tube effects	134,000	17,400	5,800	104,300
Anencephalus and similar	134,000	7,000	2,300	41,800
Spina bifridda	134,000	8,500	2,800	51,300

Table B4-5: Estimated economic value of developmental effects due to workplace exposures to Reprotoxic 1A/1B substances				
	Willingness to pay value per case	Estimates based on geometric mean of worst and best case	Best case (excludes all missing values from the Sumer data)	Worst case (includes all missing values from the Sumer data at threshold for reporting as not significant – where NS <40)
Hydrocephaly	134,000	8,300	2,800	49,700
Eye defect	46,000	1,900	600	11,600
Congenital heart defect	136200	123,900	41,300	743,700
Severe congenital heart defect	136,200	35,400	11,800	212,200
d-transposition great arteries	136,200	4,600	1,500	27,300
Ventiscular septal defects	136,200	61,600	20,500	369,400
Atrial septal defects	136,200	26,000	8,700	156,000
Atrioventicular septal defects	136,200	3,800	1,300	23,100
Tetralogy of Fallot	136,200	5,300	1,800	31,700
Hypoplastic left heart S.	136,200	4,600	1,500	27,400
Patent ductus arteriosus	136,200	7,800	2,600	46,600
Coarctation of aorta	136,200	6,700	2,200	40,200
Outflow tract defects	136,200	30,200	10,100	180,900
Conotruncal defects	136,200	14,000	4,700	84,200
Cleft palate	27,700	1,900	600	11,700
Cleft lip, w/out palate	27,700	2,900	1,000	17,600
Anorectal atresia and stenosis	136,200	5,400	1,800	32,300
Cryptorchidism	36,700	38,800	12,900	233,000
Hypospadias	21,600	5,200	1,700	31,300
Testicular cancer	136,200	900	300	5,700
Clubfoot-Talipes equinovarous	27,700	4,000	1,300	23,800
Limb deficiency (defects)	27,700	1,700	600	10,400
Craniosynostosis	136,200	4,300	1,400	26,100
Gastroschisis	136,200	4,800	1,600	28,900
Totals		9,109,500	3,036,500	54,656,700

B4.3 Potential Future Changes (Market & Legislation)

B4.3.1 Introduction

Against the above discussion of baseline numbers of workers impacted and the economic value of these impacts, this section considers future trends in the number of exposed workers and in levels of exposure (concentration). The overall trends in exposure suggest that future levels should decrease, even if production goes up. Increased worker protection measures such as local ventilation as well as substitution with compounds of lesser toxicity (a number of the substances covered in this report may be subject to Restriction in the future) will continue. Decreased exposure concentrations are thus expected and, in some cases, exposures may cease if full substitution takes place. This assumes of course that substitutes are both less toxic and that there is equal or lesser exposure (as risk= hazard * exposure).

The remainder of this chapter provides some further details regarding the trends for individual chemicals, which are summarised in Table B4-6.

Table B4-6: Trends in number of exposed workers and exposure concentrations

Substance	Number of workers trend	Exposure concentration trends
Lead	Decrease in number of exposed workers (around 2.9% per annum)	Long term trend of decreasing exposure
BPA	Increase in number of exposed workers is expected (4% per annum)[110]	Expected to be decreasing exposure concentrations
Borates	The trends depend on the sector of use. There are decreases in C20, C23, C24, C25 and C26 (between -0.4% and -1.7%). There are increases in C10, C21 and C29 (between 0.4% and 3.4%)	Exposure is expected to decrease in the future
Imidazolidine-2-thione	Likely to be a decrease	Likely to be a decrease
2-ethoxyethanol	Decreasing number of exposed workers may be likely due to the availability of alternatives	Decreasing exposure
2-(4-tert-butylbenzyl) propinolaldehyde	No information available	Exposure concentrations are low and the concentration is limited in a number of products
Dinoseb	The number of exposed workers has decreased with the substance being banned and severely restricted (Rotterdam Convention)	No information on exposure trends is available
Dodecyl phenols	No information available	No information on exposure trends is available
Organotin compounds	Decrease in the number of exposed workers (restriction under REACH)	Decrease in exposure concentrations
pTBBA	No information available	No information on exposure trends is available
Retinol	Likely to decrease slightly in 2017 and 2018	Exposure is more or less stagnant
DMF Dimethyl formamide	Likely to significantly decrease (restriction)	Exposure concentrations will decrease significantly (restriction) trending to zero

[110] In the absence of immediate regulation. Consumer pressure rather than regulation will cause "BPA free" alternatives to increase market share, hence at best leading to stagnant growth. Increased regulation will most likely lead to a decrease in BPA production as compounders/formulators will seek out alternatives.

Table B4-6: Trends in number of exposed workers and exposure concentrations		
Substance	**Number of workers trend**	**Exposure concentration trends**
NMP 1-methyl-2-pyrrolidone	Likely to significantly decrease (restriction)	Exposure concentrations will decrease significantly (restriction) trending to zero
DMAC N,N-Dimethylacetamide	Likely to significantly decrease (restriction)	Exposure concentrations will decrease significantly (restriction) trending to zero

B4.3.2 Market trends

Lead

The number of workers exposed to lead is expected to continue to decrease in the future, however, the bottom up analysis (and the figures from the Sumer survey) highlight the potential benefits that would arise from a downward revision of the current binding BLV under the CAD, which is set at 70 µg/100ml. This is an action that would be welcomed by both the industry sectors using lead (e.g. the ILA and companies signing up to Lead Action 21) and by regulators.

Over the long-term, there have been decreases in both the exposed workforce and BLL levels. This is a long-term trend which has been interrupted by increases in the exposed workforce several times. Future decreases are likely to further reduce the risk for those effects which have a threshold above the BLL caused by background exposure (e.g. reduction in median sperm concentration). BLL in the population have been decreasing even faster than occupationally related BLL.

Data from the UK show a decreasing trend over the past decade in the number of workers under medical surveillance (i.e. BLL < 40) of around 2.9% per annum, although this is a long-term trend with some intervening years showing an increase in the number of workers subject to medical surveillance due to lead exposure (HSE, 2017). Longer term data covering the period since the early 1990s show a marked decline in the numbers of male and female workers with elevated blood lead levels (>40 µg/100ml and >25 µg/100ml respectively).

For the estimated number of cases of ill health, it would be assumed that this would continue to decrease over time.

BPA

The consumption of polycarbonate in Germany and UK has been increasing by about 4% per annum, implying a corresponding increase and in the number of workers. One use where there is expected to be a decrease is in the production and use of thermal paper, which will be restricted under REACH in 2020 and reduce exposures for workers in the retail sector. Consumer pressure driven "voluntary" substitutions for BPA in so-called "BPA free" polycarbonates also will negatively affect BPA usage.

Further reductions in exposure concentrations can also expected due to the recent lowering of the indicative OELV under the CAD to 2 mg/m^3. The threshold for BPA is 4.38 mg/m^3 for impaired fertility (female) so the indicate OELV is below the threshold and the number of cases of ill health would be assumed to decrease with decreasing exposure levels.

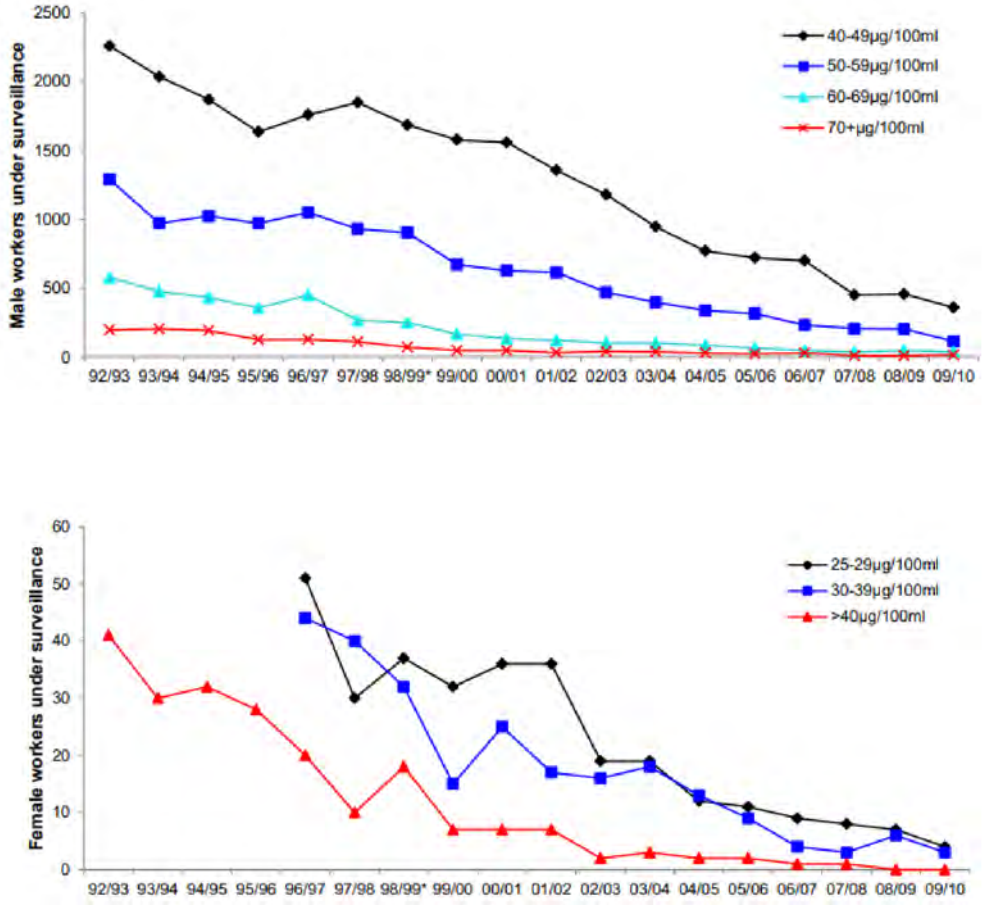

Figure B4-1: UK workers with elevated blood levels (> 25 µg/100ml)
Source: http://www.hse.gov.uk/statistics/causdis/lead/blood-lead-trend-report.pdf

Borates

For borates, the trends for number of workers differ by sector. Trend data for the sectors C10-C29 have been obtained for the time period between 2009 and 2017 and these trends are assumed to continue in the future. The future trends in the number of workers exposed to borates are as follows:

- C20 Manufacture of chemicals and chemical products: -0.6% for exposed workers of reproductive age, -0.4% for male workers of reproductive age and -1.3% for females of reproductive age;
- C23 Manufacture of other non-metallic mineral products: -1.9% for exposed workers of reproductive age, -1.7% for male workers of reproductive age and -2.0% for females of reproductive age;
- C10 Manufacture of food products: 0% for exposed workers of reproductive age, +0.4% for male workers of reproductive age and +0.6% for females of reproductive age;
- C21 Manufacture of basic pharmaceutical products and pharmaceutical preparations: +0.5% for exposed workers of reproductive age, +1.4% for male workers of reproductive age and -0.9% for females of reproductive age;
- C24 Manufacture of basic metals: -1.6% for exposed workers of reproductive age, -1.6% for male workers of reproductive age and -0.4% for females of reproductive age;

- C25 Manufacture of fabricated metal products, except machinery and equipment: -0.8% for exposed workers of reproductive age, -0.4% for male workers of reproductive age and -2.9% for females of reproductive age;
- C26 Manufacture of computer, electronic and optical products: -0.5% for exposed workers of reproductive age, -0.3% for male workers of reproductive age and -1.2% for females of reproductive age; and
- C29 Manufacture of motor vehicles, trailers and semi-trailers: +2.6% for exposed workers of reproductive age, +2.3% for male workers of reproductive age and +3.4% for females of reproductive age.

The addition of borates to the authorisation list under REACH has presently been deferred. For exposure concentrations, from consultation responses it is likely that exposure levels will continue to decrease in the future.

Imidazolidine-2-thione (ETU)

There is likely to be a downward trend in the use of ETU as an accelerator for the vulcanisation of chloroprene rubber. This is due to research into a viable alternative,[111] which was found and has been shown to perform as well, if not better than, ETU, without the toxicity.

2-ethoxyethanol

It is assumed that there has been a significant decline in the use of the substance in the EU; so the number of exposed workers would be expected to further decrease.

Exposure levels would also be assumed to decrease further in the future due to the limited use of the substance and the use of closed processes. OSHA[112] in the United States withdrew its proposed standard on Occupational Exposure to 2-Ethoxyethanol and its acetates since production and use had either ceased or was virtually limited to "closed systems" where exposure levels more than 10 years ago already were at or below the proposed permissible exposure limits (PELs). It stated that there are few, if any, remaining opportunities for workplace exposure to these glycol ethers and little or no potential for exposure in the future because of the availability of less-toxic substitutes. The use of the substance in the EU is in closed processes with no likelihood of exposure.[113] For the number of ill health cases, 8mg/m^3 is the lowest scenario is used, so the number of cases would be assumed to decrease with decreasing exposure.

The substance is also subject to a charter by the Oxygenated Solvent Producers Association (OSPA) for glycol ethers to ensure that the substances are only sold into compliant applications and uses where strict exposure control measures are in place.[114]

2-(4-tert-butylbenzyl)propinolaldehyde

There is no information available on trends on the number of exposed workers and exposure concentration trends. The substance is currently not subject to restriction or authorisation under REACH. The substance is subject to concentration limits for the substance in products which have

[111] SafeRubber. https://cordis.europa.eu/project/rcn/96346_en.html
[112] https://www.osha.gov/laws-regs/federalregister/2003-12-31
[113] https://echa.europa.eu/brief-profile/-/briefprofile/100.003.459
[114] http://www.glycol-ethers.eu/index.php/about-us/aboutus

been proposed by IFRA (International Fragrance Association) so further lowering of these limits may have decrease exposure concentrations for downstream users.[115]

Dinoseb

The number of workers exposed to dinoseb has decreased over the years. Dinoseb was previously used for agricultural uses (herbicide and insecticide) however this use has been banned in the EU before being banned for this application in 1991. Dinoseb is presently used in styrene manufacture, although there are alternatives in use so exposure could further decrease in the future.[116] Dinoseb is also on the candidate list for REACH authorisation which may further reduce exposure in the future.

There is no available information on exposure trends for occupational exposure to dinoseb although previously estimates of worker (applicators, mixers, loaders, etc.) exposure based on field measurements showed a NOEL of 3 mg/kg bw/day.[117] This exposure concentration has decreased with closed systems employed for its current use in the EU (inhalation long term DNEL of 0.4 mg/m^3).

Dodecyl phenols

No publicly available information is available on exposure trends for the dodecyl phenols. Occupational exposures to the dodecyl phenols are expected to be very low based on the compounds' physicochemical properties, use and handling patterns. From consultation responses, exposure concentrations are low. None of the dodecyl phenols are on the Candidate List, the Authorisation List or the Restrictions List under REACH.

Organotin compounds

For trends in the number of exposed workers, since 2012, a number of uses of dibutyltin dichloride have been restricted under REACH for environmental reasons. Even so, it is likely that the number of exposed workers will have reduced, and that exposure levels may have been affected as the REACH legislation has also set maximum allowed concentrations of organotin compounds in certain products. The number of exposed workers is expected to remain stagnant or continue decreasing very slightly in the future.

No information on measured occupational exposure concentrations is available. Since 2012, a number of uses of dibutyltin dichloride have also been restricted under REACH for environmental reasons, with REACH also setting maximum allowed concentrations of organotin compounds in certain products.

4-tert-butylbenzoic Acid (pTBBA)

There is no information available on future trends for the number of exposed workers and exposure concentrations. The substance is also not subject to specific legislation in the EU.

[115] IFRA (2015): p-tert-Butyl-alpha-methylhydrocinnamic aldehyde (p-BMHCA) IFRA standard. Available at: http://www.ifraorg.org/en-us/search/s/lysmeral#.W2Lu8cInaUk

[116] ECHA (2011): Comments on an Annex XV dossier for Identification of a Substance as SVHC and Responses to these comments- Dinoseb. Dated 19 November 2011. Available at: https://echa.europa.eu/documents/10162/791ab610-ceeb-4caf-b355-aad194a809ac

[117] Food and Agriculture Organisation of the United Nations (1991): Dinoseb and its salts and esters: Decision Guidance documents. Available at: http://www.pic.int/Portals/5/DGDs/DGD_Dinoseb%20and%20salts%20and%20esters_EN.pdf

Retinol

The exposure trend to retinol and retinyl palmitate remains more or less stagnant. The numbers of exposed workers and exposure concentrations are likely to decrease slightly in 2017 and 2018 due to an incident and resulting limited production at one of the main chemical manufacturing facilities in Germany.

Exposure to retinol and retinyl palmitate may decrease slightly in the future due to the implementation of regulation EU 2015/724, which sets new requirement for the use of 'vitamins, pro-vitamins and chemically well-defined substances having similar effect'. According to this regulation, the use of these substances is denied for use in water. Moreover, the use as additive in animal nutrition will be subject to additional conditions. The regulation allows for a transitional period, which ends May 26th 2025.

DMF Dimethyl formamide; NMP 1-methyl-2-pyrrolidone; DMAC N,N-Dimethylacetamide

These three so-called aprotic solvents are (about) to receive significant regulatory attention resulting in potential restrictions on use. This may lead to downward trends in both the number of workers exposed as well as exposure concentrations (e.g. due to the setting of a new OEL to reduce exposures from the use of NMP). In addition, substitution pressure within industry, such as for the use of NMP in paint strippers, may lead to even further reductions.

THTO Tetrahydrothiophene 1,1-dioxide

No data are available for this chemical. Given its recent (self)classification as R1 and it being a member of the so-called aprotic chemicals, increased regulatory scrutiny is expected.

B4.3.3 Existing and planned regulatory actions

Legislative initiatives within Member States

Within the EU, several Member States currently have legislative initiatives underway that will impact the way in which substances recognised as reproductive toxins (as well as carcinogens and mutagens) are regulated. In some cases, the member state initiatives are focused on the regulation of specific substances. For example, in France there is considerable movement for increased worker protection from reproductive toxins in the workplace. ANSES (Agency for Food, Environmental and Occupational Health & Safety) has recommended that the several CMR substances be assigned OEL values for the purposes of protecting health in the workplace (including: trichloroethylene, di-n-butylphtalate, butylbenzylphtalate, 2-ethoxyethanol (a reprotoxin described within the body of this report), and butan-1-ol).[118]

In Sweden, proposed amendments to current legislation for regulating workplace safety will increase the regulation of reproductive toxins. Specifically, the proposed amendment to the *Chemical Hazards in the Working Environment (AFS 2011:19) Regulation* would classify ethylenethiourea (CAS No. 96-45-7) as a cause of reproductive disorders.[119] The revised *Provisions on Hygienic Exposure Limits* (AFS

[118] ANSES (2017): Publication de recommandations de VLEP pour plusieurs agents cancérogènes, mutagènes et reprotoxiques (CMR) par l'Anses. Available at: https://www.substitution-cmr.fr/index.php?id=70&tx_ttnews%5Bcat%5D=1&tx_ttnews%5Btt_news%5D=227&cHash=0aa28b7a9c

[119] Arbetsmiljö Verket (2017): Förslag till föreskrifter om ändring av Arbetsmiljöverkets föreskrifter om kemiska arbetsmiljörisker. Available at:

2018:1), which takes affect 21 August 2018, will revise the OEL limits for 1,2-dibromo ethane (etyldibromid), ethylene glycol monoethyl ether, ethylene glycol monomethyl ether, carbon monoxide, and nitro benzene – all of which are recognised as reproductive toxins.[120]

In Ireland, the *2016 Code of Practice for the Chemical Agents Regulations* contains a list of proposed changes to Irish OELs (Schedule 2), including the re-classification of nickel carbonyl (CAS No. 236-669-2) as a Category 1B reproductive toxin.[121]

In other EU member states, legislative initiatives are not focused on specific substances, but rather on broader recognition of the risks associated with reproductive toxins. In Belgium, for example, the most recently published *Code of Well-Being at Work* explicitly recognises reproductive toxins to be a hazard in the workplace, at the same level as carcinogens and mutagens.[122] In Germany, the Committee on Dangerous Substances (AGS) has announced a plan to significantly lower the acceptable tolerance concentrations used to determine the risk based action plan for 2018, specifically for activities associated with hazardous substances recognised as carcinogenic, mutagenic or toxic to reproduction.[123] These initiatives are likely to impact the regulation of certain reproductive toxins in these member states in the short-term.

Several EU member states also have broad initiatives that have the potential to impact the recognition and restriction of reproductive toxins in the workplace in the longer-term. For example, in Croatia the Ministry of Labour and Pension System held a public consultation in early 2017 on a draft "National Program of Protection at Work for Period 2017-2020".[124] Reproductive toxins are mentioned in this draft document as part of the 'Vision of Development' section, in which one of the measures for the development of the population policy is to stimulate the birth rate by undertaking preventive measures affecting the reduction of mortality, disability and damage to reproductive health at work. It should be noted, however, that none of the comments associated with this draft document mentioned CMR substances in any way.

Some EU member states are still in the process of implementing existing EU legislation on CMR substances. In Bulgaria, the Ministry of Health and the Ministry of Labour and Social Policy are preparing a Transposition of Commission Directive (EC) 2017/164 of 31 January 2017 establishing the fourth list of indicative occupational exposure limit values pursuant to Council Directive 98/24/EC and amending Directives 91/322/EEC, 2000/39/EC and 2009/161/EU. The established deadline for completion of the anticipated amendment is May 2018. In Luxembourg, the Ministry of Labour,

https://www.av.se/globalassets/filer/remisser/2017_038339_forslag_till_foreskrifter_om_andring_av_arbetsmiljoverkets_foreskrifter_om_kemiska-arbetsmiljorisker.pdf?hl=%222004/37%22

[120] Arbetsmiljö Verket (2015): Hygieniska gränsvärden (AFS 2015:7), föreskrifter. Available at: https://www.av.se/arbetsmiljoarbete-och-inspektioner/publikationer/foreskrifter/hygieniska-gransvarden-afs-20157-foreskrifter/

[121] Health and Safety Authority (2016): 2016 Code of Practice for the Chemicals Agents Regulations. Available at: http://www.hsa.ie/eng/Publications_and_Forms/Publications/Chemical_and_Hazardous_Substances/Chemical_Agents_COP_2016.pdf

[122] Service public fédéral Emploi, Travail et Concertation sociale (2018): Bien-être au travail. Available at: http://www.emploi.belgique.be/bien_etre_au_travail.aspx

[123] Ausschuss für Gefahrstoffe (2018): Informationen des Ausschusses für Gefahrstoffe – AGS –zur Absenkung der Akzeptanzkonzentration gemäß TRGS 910 im Jahr 2018. Available at: https://www.baua.de/DE/Aufgaben/Geschaeftsfuehrung-von-Ausschuessen/AGS/pdf/AGS-TRGS-910.pdf?__blob=publicationFile&v=3

[124] The text of the strategy and the comments may be accessed via the platform for the online public consultations in Croatia: https://esavjetovanja.gov.hr/ECon/MainScreen?entityId=4571.

Employment and the Social and Solidarity Economy has proposed a bill for a regulation that would transpose EU Directives 2017/164/EU and 2014/27/EU into national law. This regulation aims to replace the Annex 1 of the current *Grand Ducal Regulation of 14 November 2016 concerning the protection of the health and safety of workers against the risks associated with chemical agents in the workplace*. This draft Regulation reproduces in Annex I the values from Directive 2017/164/EU; this would in turn update the Luxembourg indicative OEL list through the introduction of limits on six new substances (specifically this includes Bisphenol A).[125]

REACH Regulation

Even though REACH is not specifically aimed at occupational exposures, it can have an effect on worker's exposure to reprotoxins.[126] Substances classified as Reprotoxic 1A and 1B substances had to be registered under REACH by the first registration deadline in 2010. Some of these registration dossiers have been subject to dossier or substance evaluation under REACH. Some registered chemicals that were not classified as Reprotoxic 1A or 1B may also have been picked up in evaluation and additional reproductive toxicity data requested to be generated. In particular, many evaluations have lead ECHA to request the conduct of an extended one generation reproductive toxicity study (EOGRTS), a new standard information requirement under Annexes IX and X of REACH.

Reprotoxic 1A and 1B substances also qualify as "substances of very high concern" (SVHC) and some of them have been listed on the Candidate List and/or prioritised for authorisation and/or listed in Annex XIV (the authorisation list). Since the adoption of the SVHC roadmap by ECHA, the listing of Reprotoxic 1A and 1B substances on the Candidate List follows a Risk Management Option Analysis (RMOA) that may lead such chemicals to be listed on the Candidate List for authorisation or be subject to other risk management measures under REACH (evaluation, restrictions), CLP (harmonized classification and labelling) or under other legislation including workers' protection legislation.

There are various references to workers protection and workers' protection legislation in the REACH legislation, including in Recitals 7, 12 and 28 and in Articles 2.4(a), 9(4), 110, 128 and in Annex 1 Section 1.4. As per Article 2.4(a) of REACH, the REACH Regulation shall apply "*without prejudice to Community workplace and environmental legislation*", including the CAD and the CMD.

Several links are made between REACH and workers' protection legislation, showing that one of the objectives of REACH, and thus of the above measures, is to also protect the health and safety of workers. This is apparent in particular in Annex I, which requires the Chemical Safety Report to cover the population including workers.

Data on the numbers of substances with Reprotoxic 1A/1B classifications was pulled off of ECHA's website in early March 2018 (before the end of the final Registration deadline). This found that:

- There were a total of 194 substances registered under REACH and which held a harmonised or self-classification for being a Reprotoxic 1A/1B substance; 149 of these were not also classified as a Carcinogen or Mutagen 1A/1B;

[125] The last three substances in this list were updated in previous amendments to EU CMR directives. For acrylic acid, Directive 2017/164/EU now provides a short-term exposure limit for a reference period of one minute. The short-term exposure limit values for this chemical agent are therefore set out in Annex I to the draft Grand-Ducal Regulation. For some substances, the draft Grand-Ducal Regulation takes into consideration the possibility of skin penetration to ensure the best possible level of protection.

[126] EU OSHA (2017): State-of-the-art report on reproductive toxicants. Available at: https://osha.europa.eu/en/tools-and-publications/publications/summary-state-art-report-reproductive-toxicants/view

- Of these, 7 had been subject to REACH Restrictions, and 8 had been subject to Authorisation. A further 35 were at that time on the Candidate List, and 9 were being evaluated through the Community Rolling Action Plan (CoRAP – see also below).

Since this time, Restrictions have been adopted on, for example, NMP and ECHA continues to evaluate new substances for Candidate Listing and Prioritisation. It is clear therefore that REACH will continue to place regulatory pressure on the use of Reprotoxic 1A/1B substances through both Restriction and Authorisation.

Public Activities Coordination Toolbox (PACT)

The Public Activities Coordination Toolbox (PACT) is used by ECHA to provide notice of substances that are being considered by Member State Authorities or ECHA for further regulatory risk management. PACT lists the substances for which a RMOA or an informal hazard assessment for PBT/vPvB properties or endocrine disruptor properties is either under development or has been completed since the implementation of the SVHC Roadmap commenced in February 2013.

Assessments documented in the PACT do not have direct legal implications or regulatory relevance. To gain legal and regulatory relevance the substance also has to undergo one or more formal risk assessment and decision-making processes under REACH and/or CLP.[127] In terms of worker exposure to reprotoxic substances, RMOA and informal hazard assessments in the PACT would have no direct effect on workers exposure, although subsequent follow-up actions may.

Community Rolling Action Plan (CoRAP)

The CoRAP is used by ECHA to clarify if a substance is an actual risk to human health and or/the environment. The outcome of the evaluation by a member state can be either that no action is required or follow-up action, e.g. EU-wide risk management measures.[128] In terms of worker exposure, CoRAP would have no direct effect on exposure; however, evaluations carried out under the CoRAP may result in follow up action that may have an effect.

CoRAP specifies the substances for evaluation over a three-year period with risk-based criteria (exposure information, hazard information and tonnage) used to determine the substances to be evaluated. ECHA and member state authorities perform this process. For the substances that meet the CoRAP criteria for inclusion, not all the substances may be evaluated. This depends on whether a further information request at the end of the evaluation would aid in clarifying the initial concern for the substance. After the risk-based criteria, ECHA and member states will then identify substances to be included in the CoRAP with member states expressing their interest in evaluating a substance. The final CoRAP (which indicates the initial concern and designates the member state to perform the evaluation) is then adopted after member state consultation and the opinion of the Member State Committee of ECHA.[129]

[127] ECHA (2017): Status and purpose of PACT. Available at https://echa.europa.eu/addressing-chemicals-of-concern/substances-of-potential-concern/pact/status-and-purpose

[128] ECHA (2017): REACH CoRAP and Substance Evaluation. Available at https://echa.europa.eu/support/qas-support/browse/-/qa/70Qx/view/scope/REACH/corapandsubstanceevaluation

[129] ECHA (2017): Community rolling action plan. Available at https://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Other relevant regulations

A variety of other regulations may have an effect on worker exposure o R1A /1B substances.

- **Biocides Products Regulation (BPR):** Regulation (EU) 528/2012 concerns biocidal products placed on the EU market.[130] The purpose of this regulation is to ensure a high level of protection for humans and the environment and to improve the functioning of the biocides market in the EU. As part of the regulation, the active substances in the biocidal products need to be approved and biocidal products need to be authorised before they can be placed on the market.[131]

- **Cosmetic Products Regulation (EC) No 1223/2009:** The Cosmetic Products Regulation (EC) No 1223/2009 concerns the rules for the marketing of cosmetic products and to ensure human health and the internal market functioning (Official Journal of the European Union, 2009).[132] Some reprotoxins are subject to the Cosmetic Products Regulation.

- **Rotterdam Convention:** The Rotterdam Convention covers industrial chemicals and pesticides that have been either banned or severely restricted for health or environmental reasons and have been notified by parties for inclusion in the PIC (Prior Informed Consent) procedure. The PIC procedure concerns the international trade of these substances and provides an exchange of the national decision making process on the import/export of these substances and for discussing these decisions to parties.133 Dinoseb has been banned under the Rotterdam Convention.

B4.3.4 Regulatory actions on substances

The regulatory statuses of the shortlisted substances (past and present) are discussed in the individual annexes:

- **Current exposure – REACH**: Substances that are not on the authorisation list at present are: borates; lead di(acetate); trilead dioxide phosphonate; phenol compounds; retinol compounds; dinoseb; imidazolidine-2-thione; 4-tert-butylbenzoic acid; 2-ethoxyethanol; and 2-(4-tert-butylbenzyl)propionaldehyde.

- **Restriction under REACH**: For lead, lead metal as a substance is prohibited to be supplied to consumers as a substance and in mixtures (which includes solders and other alloys), where the individual concentration is greater or equal to 0.3% for lead metal in massive form and for concentrations which are greater or equal to 0.03% for mixtures containing lead powder. For restricted substances and mixtures containing lead covered by entry 30 of REACH, their

[130] Official Journal of the European Union (2012): Regulation EU 528/2012 of the European Parliament and of the Council of 22 May 2012. Available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:167:0001:0123:en:PDF

[131] ECHA (2017): Understanding BPR. Available at https://echa.europa.eu/regulations/biocidal-products-regulation/understanding-bpr

[132] Official Journal of the European Union (2009): Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:342:0059:0209:en:PDF

[133] Rotterdam Convention (2010): Overview. Available at: http://www.pic.int/TheConvention/Overview/tabid/1044/language/en-US/Default.aspx

packaging must be marked 'Restricted to professional users'. [134] The concentration of lead is also limited in jewellery with jewellery that contains lead (metal) at a concentration of equal or more than 0.05% not to be placed on the market, although there are some exemptions.[135] There are some further possible restrictions on the use of lead and its compounds in shot (greater than 1 wt. %) and in PVC which could have an impact on worker exposure.[136]

- **Biocidal Product Regulation and Plant Protection Product Regulation:** Boric acid, disodium tetraborate, anhydrous and diboron trioxide are all subject to the Biocidal Product Regulation for use as a wood preservative.[137] The use of borates for biocidal applications potentially involves a number of occupationally exposed workers. Boric acid, disodium octaborate, and dinoseb (covered by dinoseb, its acetate and salts) have formally not been approved under the PPPR for use in plant protection products.[138]

- **Rotterdam Convention:** Dinoseb (one of the shortlisted substances) has previously been used as a pesticide but is now banned. This means that the number of exposed workers has decreased over time with its use now only taking place in closed systems for polymerisation (thus, the number of exposed workers has decreased and so this has had an impact on exposure). The organotin substances are also listed in the Rotterdam Convention and their uses are severely restricted. This will have impacted on worker exposure, as the uses of these substances will have decreased.

A number of the substances are on the candidate list for authorisation, as shown in the Table B4-7 below. If any of these were to be included in Annex XIV, this would be likely to impact on any worker exposures taking place at levels above the threshold for effects, as companies would be required to minimise worker exposure. Additional conditions and monitoring arrangements would likely be included in the authorisation decision and eventually the substance would have to be substituted.

With respect to future Restrictions under REACH, Bisphenol A will be restricted under Annex XVII to REACH. This restriction concerns the concentration of BPA in thermal paper where the concentration of BPA shall not exceed 0.02% by weight for thermal paper placed on the market after 2nd January 2020.[139] BPA has also been identified as a SVHC under Article 57 (1) of REACH for human health.[140]

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[134] ILA REACH (2016): New restrictions and labelling requirements affect lead and lead-containing mixtures from March 1, 2018. Dated Jan 23, 2018. Available at: https://ila-reach.org/2018/01/new-restrictions-and-labelling-requirements-affect-lead-from-march-1-2018/

[135] ECHA (undated): Annex XVII to REACH- Conditions of restriction. Available at: https://echa.europa.eu/documents/10162/3f17befa-d554-4825-b9d5-abe853c2fda2

[136] ECHA (2018): Submitted restrictions under consideration. Available at: https://echa.europa.eu/restrictions-under-consideration/-/substance-rev/17005/term?_viewsubstances_WAR_echarevsubstanceportlet_SEARCH_CRITERIA_EC_NUMBER=231-100-4&_viewsubstances_WAR_echarevsubstanceportlet_DISS=true

[137] ECHA (2018): Biocidal Active Substances. Available at: https://echa.europa.eu/information-on-chemicals/biocidal-active-substances

[138] ECHA (2018): Biocidal Active Substances. Available at: https://echa.europa.eu/information-on-chemicals/biocidal-active-substances?p_p_id=echarevbiocides_WAR_echarevbiocidesportlet&p_p_lifecycle=0&p_p_col_id=column-1&p_p_col_pos=1&p_p_col_count=2&_echarevbiocides_WAR_echarevbiocidesportlet_rml_id=100.013.751

[139] ECHA (undated): Annex XVII to REACH- Conditions of Restriction. Available at: https://echa.europa.eu/documents/10162/370b5de7-9507-f1b4-edc6-80ef2e5cd781

[140] ECHA (2017): Agreement of the Member State Committee on the Identification of 4,4'-isopropylidenediphenol (Bisphenol A) as a Substance of Very High Concern. Available at: https://echa.europa.eu/documents/10162/ac9efb97-c06b-d1a7-2823-5dc69208a238

For worker (primarily cashiers) and consumer exposure this will have a direct effect in the future as the concentration of BPA they may be exposed to in thermal paper will decrease.

B4.3.5 Conclusions

The overall trends in exposure suggest that levels of exposure into the future for several of the substances should continue to decrease, due to the increasing use of collective worker protection measures and actions taken by employers under the CAD, as well as substitution to substances of lower toxicity, whether voluntarily or due to regulatory pressures. In particular, for key substances such as lead, action is being taken by the relevant sectors to reduce worker exposures with this coming on top of decreases in the number of exposed workers. Furthermore, the potential benefits of a lower binding BLV for lead under the CAD is recognised by the industry as well as by authorities. This includes borates, 2-ethoxyethanol, organotins, DMF and Dimethyl formamide, NMP and DMAC.

Regulatory pressures will also stem from ongoing actions at the Member State level under OSH legislation with respect to the revision or introduction of national OELs for reprotoxic substances. Such actions may be reinforced by REACH. Of the 194 substances registered as Reprotoxic 1A/1B substances (as of March 2018), 68 have a harmonised classification for this property; 16 of these already subject to REACH Restrictions or Authorisation, and a further 35 are on the Candidate List and 9 were on the Community Rolling Action Plan.

Table B4-7: Regulatory actions (as of 7th August 2018)				
Substance/group	EU Legislation			National legislation
	REACH Authorisation	REACH Restriction	Other EU legislation	Other actions
Bisphenol A	Included on candidate list (Date of inclusion - 12/01/2017) CoRAP evaluation concluded in 2012: Need for follow up regulatory action at EU level and identification as SVHC	Favourable opinion adopted - Shall not be placed on the market in thermal paper in a concentration equal to or greater than 0,02 % by weight after 2 January 2020 (Date of restriction decision – 12/12/2016) PACT – RMOA identified is was appropriate to initiate regulatory risk management action (13/06/2017 (Germany))	Food contact materials (not allowed to be used as additive or polymer production aid; allowed to be used as monomer or other starting substance or macromolecule obtained from microbial fermentation; 0.6 mg/kg specific migration limit)	Banned in plastic bottles and packaging containing food for babies and children under three years old Austria and Germany ban BPA in pacifiers and teething rings In Belgium, Sweden and Denmark, it is also banned in other materials that come into contact with food intended for infants and children under three years. France has banned BPA in all food packaging, containers and utensils.
Diboron trioxide	Included on candidate list (Date of inclusion - 18/06/2012)	-	-	-
Disodium tetraborate, anhydrous	Included on candidate list (Date of inclusion - 18/06/2010)	-	Approved under BPR (PT-8)	-
Boric acid	Included on candidate list (Date of inclusion - 18/06/2010)	-	Not approved under PPPR	-
Disodium octaborate	Included on candidate list (Date of inclusion - 27/06/2018)	PACT – RMOA identified is was appropriate to initiate regulatory risk management action (12/12/2017)	Approved under BPR (PT-8) Not approved under PPPR	-
Perboric acid, sodium salt	Included on candidate list (Date of inclusion - 16/06/2014)	-	-	-
Lead	Included on candidate list (Date of inclusion - 27/06/2018)	Favourable opinion adopted – Restriction on lead in jewellery Registry of restriction intentions include: Restrictions for lead and its compounds used in lead shots over wetlands (Favourable opinion adopted by RAC and SEAC – lead and	RoHS Directive (Lead maximum concentration 0,1%, with certain exemptions) Cosmetic Regulation (prohibited in cosmetic products) Toy Safety Directive (limit values and migration limits)	-

		lead compounds shall not be used in gunshot for shooting with a shot gun within a wetland or where spent gunshot would land within a wetland; and lead gunshot shall not be in the possession of persons in wetlands) PACT – RMOA identified is was appropriate to initiate regulatory risk management action (23/09/2014 and 29/09/2017)	Batteries and accumulators directive (those containing >0,004% lead requiring lead labelling) End-of-life vehicles (lead prohibited, some materials and components exempt) Packaging and packaging waste (concentration limits for lead in packaging, 100 ppm, lead crystal being exempt) Food contact materials (Not more than 2 mg/kg of plastic) Commission Directive (EU) 2015/1787, maximum drinking water concentration of lead µg/l	
Lead di(acetate)	Included on candidate list (Date of inclusion - 16/12/2013)	-	Cosmetic Regulation (prohibited in cosmetic products) Prior Informed Consent (PIC) (Rotterdam Convention) – severely restricted industrial chemical for public use	-
Trilead dioxide phosphonate	Included on candidate list (Date of inclusion - 19/12/2012)		Cosmetic Regulation (prohibited in cosmetic products) Prior Informed Consent (PIC) (Rotterdam Convention) – severely restricted industrial chemical for public use	-
Phenol, dodecyl-, branched	CoRAP evaluation under development (endocrine disruptor)	PACT – RMOA substance evaluation under development (endocrine disruptor)	-	-
Phenol, dodecyl-, sulfurized, carbonates, calcium salts	-	PACT – RMOA substance evaluation under development (CMR)	-	-
Phenol, dodecyl-,	CoRAP evaluation conclusion	PACT – RMOA Substance evaluation under	-	-

sulfurized, calcium salts, overbased	under preparation. Further information was requested from registrants (CMR)	development (toxic for reproduction)		
Phenol, dodecyl-, sulfurized, calcium salts	CoRAP evaluation concluded in 2016 (toxic for reproduction): Need for follow up regulatory action at EU level (RMOA) and identification as SVHC	PACT – RMOA substance evaluation under development (toxic for reproduction)	-	-
Phenol, dodecyl-, branched, sulfurized	-	-	-	-
Tetrapropenyl phenol	CoRAP evaluation under development (endocrine disruptor)	PACT – RMOA substance evaluation under development (endocrine disruptor)	-	-
Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate)	-	PACT – RMOA substance evaluation under development (CMR)	-	-
Retinol	-	PACT – RMOA according to authority's assessment not PBT/vPvB	-	-
Retinyl palmitate	-	-	-	-
Dibutyltin dilaurate	-	-	Prior Informed Consent (PIC) (Rotterdam Convention) – severely restricted industrial chemical for public use	-
2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetetradeconoate (DOTE)	Included on candidate list (Date of inclusion - 17/12/2014)	PACT – RMOA identified is was appropriate to initiate regulatory risk management action (23/09/2014)	Prior Informed Consent (PIC) (Rotterdam Convention) – severely restricted industrial chemical for public use	-
Dibutyltin oxide	-	-	Prior Informed Consent (PIC) (Rotterdam Convention) – severely restricted industrial chemical for public	-

			use	
Dibutyltin bis(2-ethylhexanoate)	-	-	Prior Informed Consent (PIC) (Rotterdam Convention) – severely restricted industrial chemical for public use	-
Dinoseb	Included on candidate list (Date of inclusion - 19/12/2012)	-	Not approved under PPPR Prior Informed Consent (PIC) (Rotterdam Convention) – banned: other pesticide including biocides; industrial chemical for public use; pesticide in the group of plant protection products	Health Canada have derived an acceptable daily intake (ADI) as 0.001 mg/kg bw per day. The MAC (maximum acceptable concentration) for dinoseb in drinking water has been calculated as 0.01 mg/L. US EPA has derived an oral Reference dose of 0.001 mg/kg bw/day, based on a reproductive LEL of 1 mg/kg/day
Imidazolidine-2-thione	Included on candidate list (Date of inclusion - 16/12/2013)	-	-	-
4-tert-butylbenzoic acid	-	PACT – RMOA according to an authority there is no need to initiate further regulatory risk management action at this time		-
2-ethoxyethanol	Included on candidate list (Date of inclusion - 15/12/2010)	-	Regulated through European Directives which evaluate and control the risks of substances known to be in the environment (793/93/EC) and the Solvents Directive (99/13/EC)	Releases of 2-Ethoxyethanol are controlled through the UK Pollution, Prevention and Control (PPC) Regulations. As a VOC, levels in air are also regulated through the UK National Air Quality Strategy. At an international level, 2-Ethoxyethanol is regulated through the UN/ECE Convention on Long-Range Transboundary Air Pollution and the Basel Convention concerning the transboundary movement and disposal of hazardous wastes.
2-(4-tert-	CoRAP evaluation follow up	PACT – RMOA:	Cosmetics Regulation (When the	-

butylbenzyl)propionaldehyde (BMHCA)	(CMR)	Substance evaluation under development (endocrine disruptor) Not PBT/vPvB according to authority's assessment	substance is present in a concentration above 10 ppm for leave-on products and above 100 ppm for rinse-off products, the presence of the substance must be indicated in the list of ingredients) SCCS concluded that the BMHCA is not safe for use as fragrance ingredient in cosmetic leave-on and rinse-off type products	
Sources: ECHA (2018): Information on Chemicals. Available at: https://echa.europa.eu/information-on-chemicals; accessed 7th August 2018				

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Annex 1 Methodology

X1.1 Approach to the derivation of no-effect thresholds and DRRs

X1.1.1 Introduction

Based on the identification of relevant studies following a literature review, we calculated thresholds (not to be construed as legal thresholds) and dose response relationships for 15 selected chemicals and groups. In order to be as comprehensive as possible, we depended on abstracts from studies where necessary.

The list of compounds and groups includes:

- Borates (inorganic)
- BPA
- Lead (Inorganic compounds)
- Retinols
- Tert-butylbenzylpropanolaldehyde
- 4-Tertbutyl benzoic acid
- Dodecyl phenols
- 2-Ethoxyethanol
- Dinoseb
- Ethylenethiourea
- Dibutyl organotin compounds
- 1-Methyl-2-pyrrolidone (NMP)
- N,N-dimethylformamide (DMF)
- N,N-Dimethylacetamide (DMAC)
- Tetrahydrothiophene -1,1-dioxide

The analysis is focused on statistically significant effects that are also biologically relevant: random statistical associations were ignored. After all, a 95% significance level (oversimplified) implies 5% false positives. Examples of ignored effects include:

- Increase in effects observed that were still below the historical control rate;
- In the BPA Clarity study [141]effects that were only observed in the stop dose study but not in the continuous dose study;
- Outliers: statistically significant results that were surrounded by non-significant results, e.g. a statistically significant increase in Effect A observed at dose 2 but neither at dose 1 nor doses 3 and 4, and does not exhibit a statically significant overall trend; and
- Effects that are reprotoxic but clearly not related to occupational exposure, e.g. effects seen following exposure during (late) pregnancy.[142]

[141] NTP CLARITY-BPA core study, 2018

[142] This assumes that workers are not working till late in pregnancy. It is noted that this is a simplification and, in some instances, workers may work until late stages in pregnancy.

X1.1.2 Approach to derivation of threshold and Dose-Response Relation factors (DRRs)

The process of deriving the thresholds and DRRs comprises the following steps:

- Step 1: Listing all potentially relevant effects;
- Step 2: Grouping the identified effects and determination of human relevance;
- Step 3: Determination of a no-effect threshold for a typical worker;
- Step 4: Determination of occupational relevance;
- Step 5: Determination of an occupational thresholds & Dose-Response Relationships (DRRs); and
- Step 6: Conclusions on thresholds & DRRs

Step 1: List of All Potentially Relevant Effects

The effects listed have to be both biologically relevant and statistically significant. As noted above, statistical significance does not imply biological relevance, i.e. a spurious statistical effect cannot be assumed to be biologically relevant unless the effects are continuous throughout the dose range and dose-response relationship(s) can be established. On the other hand, dose response relationships that show statistically significant trends are most likely (95/5% rule) biologically relevant even though none of the increased responses at individual doses reach a level of statistical significance. A true dose response relationship is a hallmark of biologically relevant effects, so statistically significant trends in dose-response relationships are very important as indication of an association between dose and response at the beginning of the dose-response curve before frank statistically significant effects can be observed.

Step 2: Grouping of the identified effects & determination of relevance to humans in case of experimental animal data

Effects were grouped according to biological category, e.g. all sperm related abnormalities. These groupings aid the selection of the most relevant dose response curve for each monetisable effect, resulting in selection of the "strongest" effect within each category, i.e. that effect with the lowest threshold and/or steepest dose-response relationship. Selection of the strongest effect is basically a statistical reality; e.g. if effects with a similar threshold have dose response slopes of 1.00, 0.05 and 0.01 only the 1.00 slope will contribute to the overall dose-response. (As per our discussion elsewhere, the likelihood that the accuracy of our estimates will even approach 5% is rather low.)

In addition, experimental animal data were screened for their potential relevance to humans.

Step 3: Determination of a no-effect threshold for a typical worker

Individual study results were examined to determine a study threshold. Where a NOAEL for an effect was identified, the NOAEL was selected as the threshold. Where only a LOAEL was identified, the threshold equalled the LOAEL/10. In all cases these thresholds were converted to human equivalent inhalation exposures and where needed/justified, adjusted to a 40 hour workweek (5 days of 8 hours each). The average inhalation volume for an 8 hour work shift was assumed to be 10 m^3 and the average weight was assumed to be 70 kg, both standard assumptions (ECHA, 2012)[143]. Allometric

[143] ECHA 2012 Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health

factors for extrapolation of human data from animal data were taken from SCOEL (SCOEL, 2017)[144]. Considering all these factors: study threshold (mg/kg bw/day), human body weight (70 kg), species conversion factor and average inhalation air volume for an 8 hour shift (10 m^3), a converted threshold was derived (in mg/m^3)when extrapolating from an oral study dose to inhalation parameters as described in ECHA, 2012 (see the figure below).

Dermal exposures are possible and where true inhalation studies were used, are accounted for. Generally dermal exposures cannot be easily quantified (very few animal studies are conducted using dermal application/dosing) and are assumed to be protected against via appropriate PPE.

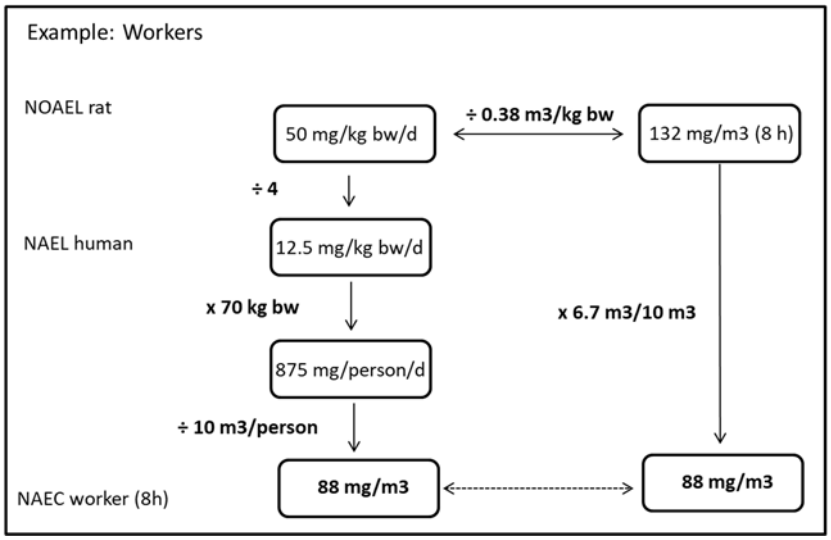

Figure X1-1: Extrapolation for oral dose to inhalation exposure rates: Taken with slight modifications from 'Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health (ECHA, 2012)

For each effect, available % responses for each dose group were determined and converted to human values. The % response for effect was calculated as:

> ***% response = conservative (maximum) % response for effect – control/next lower dose (NOAEL) % response***

Based on % response seen in doses, the dose showing minimum % significant response (or highest dose for statistically significant dose-response relationship) was considered as Effect level LOAEL (for that effect).

echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258

[144] SCOEL 2017 Methodology for derivation of occupational exposure limits of chemical agents. The General Decision-Making Framework of the Scientific Committee on Occupational Exposure Limits (SCOEL) https://publications.europa.eu/en/publication-detail/-/publication/3c8ef3e0-48fc-11e8-be1d-01aa75ed71a1/language-en

Calculations for determination of no-effect threshold:

1) For each effect, available % responses in each dose group were determined.
2) % response for effect was calculated:
   % response = conservative (maximum) % response for effect – control/next lowest dose (NOAEL) % response[145]
3) Based on % response seen at doses, dose showing first significantly increased % response was considered as Effect level LOAEL (for that effect) or for a significant dose-response relationship (no statistically significant individual doses) as the highest dose tested
4) Threshold value was calculated as,

$$Threshold\ value = NOAEL\ observed\ or\ \frac{LOAEL\ observed}{10}$$ [146], [147]

5) For extrapolation from animal studies to human, the following conversions were involved[148]:
   Interspecies conversion factor: from rat to humans: 4 and mice to humans: 7
   Route-to-route extrapolation factor: from oral to inhalation: 1
6) Final threshold were calculated using conversion factors.

$$converted\ threshold = \frac{study\ threshold * 70}{species\ conversion\ factor * 10}$$

These thresholds are overall thresholds: they account for background exposure PLUS occupational exposure. In other words, background concentrations have to be added to occupational exposure concentrations to determine whether a threshold has been exceeded. In most cases background exposure is negligible relative to occupational exposure but not always e.g. lead.

Step 4: Determination of occupational relevance

This involves screening out effects identified in studies that may not be relevant to occupational exposure, e.g. studies of dietary or environmental exposures of certain groups of people. Exceptions were made for essential nutrients such as retinol (Vitamin A) where nutritional status affect occupational effects. Occupational relevance was determined by effect(s) observed in the progeny and reproductive physiology of adult males and females – purely developmental effects were excluded unless they could be shown as being derived from exposure prior to pregnancy, during early (undetected) pregnancy or as a result of depletion of body stores of a chemical resulting in continuous exposure during pregnancy or post-delivery, even in the absence of continuous exposure i.e. removal from exposure associated work environment.

Step 5: Development of occupational thresholds and DRRs

No-effect thresholds had been previously converted to human occupational thresholds as shown above**.** All exposures were converted to inhalation exposure estimates regardless of the route of

[145] Control values were used instead of NOAEL values if no NOAEL was available (i.e. NOAEL calculated as LOAEL/10) or if a statistically significant trend only was observed. In all other cases NOAEL values were used.
[146] Only if no NOAEL can be identified, would one choose LOAEL/10.
[147] The most "conservative" value as per Dourson, ML and Stara, JF. 1983. Regulatory history and experimental support of uncertainty (safety) factors. Regul. Toxicol. Pharmacol. 3:224–238
[148] Guidance on Assessment Factors to Derive a DNEL, Technical Report No. 110, Brussels, October 2010. European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-110-Guidance-on-assessment-factors-to-derive-a-DNEL.pdf

exposure within studies. Dermal exposure in animal studies was rarely encountered hence no consideration of dermal exposure has been made**. <u>No account was taken of existing occupational thresholds or biological limit values</u>**. Thresholds were calculated solely based on data identified as part of this study. Nonsensical thresholds were eliminated at the final stage where thresholds associated with for instance 1000-fold dose response rates were eliminated. These instances are discussed in detail for each chemical where appropriate. No safety or assessment factors were applied. Thresholds assume that occupational and background exposures are added together to derive one composite exposure estimate.

Calculations for determining dose response curve:

Occupational (Dose Response Relationships) DRRs are derived for the chemicals that have an occupational threshold. The DRRs are postulated as wholly independent of the threshold, i.e. even if a different threshold is selected the DRR holds true (see the figure below). One would have to limit the difference of a new threshold to about 25% of the original threshold. This is equivalent to saying the amount of "noise" in the dose-effect response is non-measurable/"non-significant" at the selected threshold. This results in an overestimate of the effects at lower concentrations just above the selected threshold especially. Alternatively, one can repeat the whole calculation for probably no "improvement" in reliability of estimate. Two values are given in the tables: the threshold and the DRR converted value. The slope only holds true between the threshold and the threshold plus DRR converted value, included as Maximum Range of applicability i.e. the sum of threshold and range.

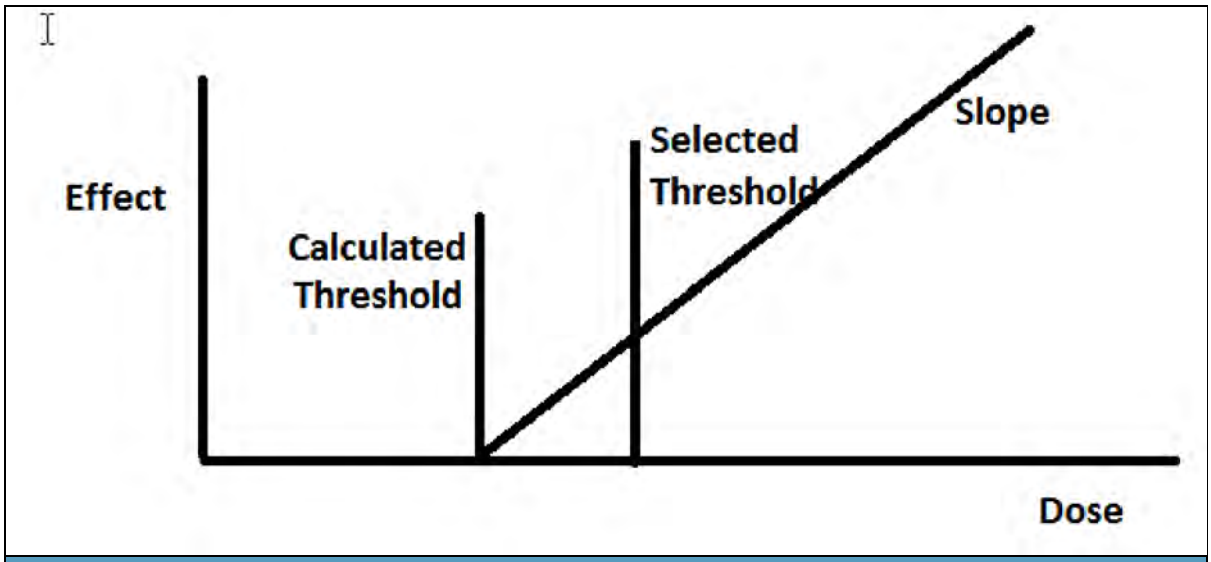

Figure X1-2: DRRs are independent of threshold

1) Dose response is calculated as
   Dose response (in %) = {effect level LOAEL– effect level NOAEL[149,150]} /effect level NOAEL x 100 (%)[151]

[149] Or control value as discussed above.
[150] If effect at NOAEL or control was "0", the value of "1" was arbitrarily assigned.
[151] If data is already expressed in % the conversion to % is unnecessary, i.e. do not multiply by 100%

2) Taken into consideration are previously calculated exposure concentrations, including conversion factors to extrapolate route to route and from animal studies to humans,

$$converted\ dose = \frac{study\ dose * 70}{species\ conversion\ factor * 10}$$

3) Slope to be calculated as,

$$\boldsymbol{slope} = \frac{\%\ \boldsymbol{dose\ response}}{\boldsymbol{converted\ dose}}\ \text{in } \%/mg/m^3$$

In words, the slope equals the percentage over control response (i.e. 2/50 vs 4/50 would result in a 100 % increase) at a certain dose, expressed as % / (mg/m3). When % response was not available in the study, SLOPE could not be calculated for that effect.

Step 6: Conclusions: occupational thresholds and DRRs

This section provides the final conclusions, i.e. effects that have not been screened out in previous sections because they are not relevant to human occupational exposure and for which occupational thresholds and DRRs could be developed. In addition, one eliminates those effects which are marginal with regard to reprotoxicity such as absolute organ weight, even they are related to testis.

A simple quality control check was performed for all studies considered in this study, including:

- Multiple studies on same endpoint e.g. 3 reduced relative testis weight: we eliminate all but the most "sensitive" one
- Elimination of all effects based on changes in absolute organ weights especially when weight reduction occurs in parent/offspring; relative organ to weight ratios are retained
- Elimination of slopes of 0.001 and below no effect will come of this
- Elimination of the occasional study that is irrelevant to occupational exposure, i.e. lead exposure among highways
- Elimination of slopes over 10,000; obviously an "error"

Further steps: Calculate nominal responses for each threshold & DRR

One of the major problems with extrapolating data from animals to humans may be that even though one has selected for biological and statistical significance, results may still be nonsensical. Incomplete epidemiological studies can be conducted in such a way to show correlations without controlling for confounding exposures such as co-exposure to other chemicals with known toxicity. An example would be cardiac effects correlated only to lead exposure as measured via blood lead levels (Lanphear BP et al., 2018)[152]. The dose response curves for cardiotoxicity derived there would indicate very high percentage mortality from cardiac disease in workers occupationally exposed to lead (even at low levels of lead) which based on existing epidemiological data is indeed nonsensical.

Statistical significance only works up to a certain level – the probabilities of a positive response may approach 100% or 1, but they will never equal it. Hence at a 95% statistically significant response ($p<0.05$) there exists a 5% probability that the result is not significant (oversimplified). Large studies especially with lots of significant results will therefore always include results that are labelled statistically significant but represent chance events that are not of biological relevance. Conversely a small percentage of biologically-relevant effects may not be designated as statistically significant.

[152] Lanphear, BP et al, The Lancet **3(4)** PE177-E184, 2018**.** Low-level lead exposure and mortality in US adults: a population-based cohort study

Checks have been performed to eliminate nonsensical results. For example, in the BPA example, DRRs approaching negative 1000 are obviously nonsensical as they imply that exposure to 1 mg/m^3 of a chemical would result in a 10 fold decrease of the base rate.

There are significant uncertainties in the assessment: all calculations are made using at a minimum the following assumptions:

- Animals and humans respond in a similar manner to a given chemical
- Response rates in humans and animals are assumed to be identical following equivalent exposures i.e. similar sensitivity (not always the case e.g. lead)
- Effects are consistent across an entire population (i.e. ignore differential sensitivity across a population)
- Epidemiological studies of populations in many cases reflect rates found in the working population; the rates in the general population are generally higher, reflecting the so-called healthy worker effect
- Exposures can be calculated based on biological exposure measurements/parameters (i.e. their validity of a correlation with exposure levels has been established e.g. lead but not so much for BPA)
- Assumption of a linear dose-response between threshold and LOAEL.
- NOAEL can be derived from LOAEL by dividing by 10, the most conservative assumption but most likely too high in most cases[147].
- Extrapolation of data from animal to human data are exact, i.e. allometric factors are estimated correctly.

As noted in the body of the text, the data are generally not normally distributed (often grossly so, especially for exposure data) so where possible we have used the geometric mean or median of the data to extrapolate effects. Differences between mean and median approaching 2 orders of magnitude have been reported indicating that the data are markedly not normally distributed, making use of an arithmetic mean generally not acceptable. Where this was not possible i.e. animal studies, we can assume that the resolution is often larger than 50% of control values (i.e. only effects 50% larger than control values reach significance) indicating uncertainties so that at a minimum the error rate is greater than 25%, (simplified as two standard deviations) except for very large effects with very low control rates. As previously indicated, in the draft BPA Clarity study[153], statistically significant effects were observed in the stop dose and interim sacrifices studies which were not observed in the continuous full study. That alone gives an indication of how "reliable" statistically significant data are.

X1.2 Approach to the quantification and valuation of health effects

Literature review

Literature review was undertaken to identify:

- Disability weights for each of the relevant health effects;
- Direct and indirect costs of ill-health, relating to each of the relevant health effects;
- Average proportion of events by severity, e.g. low birth weight of mild, moderate and severe severity;
- Average time spent with disability, for each of the relevant health effects;

[153] Draft NTP research report on the CLARITY-BPA core study: A perinatal and chronic extended-dose-range study of Bisphenol A in rats; Research report 9, National Toxicology Program, February 2018. https://ntp.niehs.nih.gov/ntp/about_ntp/rrprp/2018/april/rr09peerdraft.pdf

- Average years of life lost for each of the relevant health effects; and
- Relevant willingness to pay values.

A large number of studies were reviewed and those that were used for referenced, are quoted in the text and tables.

Population

The population to which we are applying our valuations is the EU workers exposed to the identified substances, or as calculated for the top down analysis. The valuations are applied to the estimated number of cases of ill-health derived for these populations. This is a representative sample of the total EU workers exposed to Reprotoxic 1A/1B substances, and is therefore be extrapolated to give an estimate for this total EU worker population.

Model structure

The perspective of the model is a societal one, taking into account intangible costs, valued using disability weights, direct costs of medical treatment and indirect costs, such as productivity losses. The key features of the analysis are summarised in Table X1-1.

Table X1-1: Key features of the model

Factor	Chosen value	Rationale/reference
Time horizon	Lifetime	Time period of which all effected individuals will have died
Average life expectancy – male	75 years	Eurostat
Average life expectancy – female	82 years	Eurostat
Health effects measured in	DALYs	As used by WHO
Value of a DALY	€100,000	Highfill and Bernstein (2014)
Discount rate	0.040	Standard rate for EC impact assessment
Exchange rate £ to €	1.14	January 2019
Perspective	Societal	Includes intangible, direct and indirect costs of ill-health, as Better Regulation Guidelines

Eurostat (2018) *https://ec.europa.eu/eurostat/statistics-explained/index.php/Mortality_and_life_expectancy_statistics*
WHO (2003) *https://www.who.int/quantifying_ehimpacts/publications/9241546204/en/*
Highfill and Bernstein (2014): Using Disability Adjusted Life Years to Value the Treatment of Thirty Chronic Conditions in the U.S. from 1987-2010. Available at: https://www.bea.gov/papers/pdf/highfill_bernstein_2014_dalysall.pdf
European Commission (2017) *https://ec.europa.eu/info/sites/info/files/better-regulation-guidelines.pdf*

Monetary valuation included converting the estimated DALYs to a monetary value based on the assumption that one DALY = €100,000 in intangible health damages. This assumption is consistent with recent work on the benefits of introducing BOELVs into CMD for a range of chemical agents.

Stassen et al. (2007)[154] estimate that the cost of a DALY for severe morbidity health effects is €87,000. According to a website about persistent organic pollutants[155], the value of a DALY in the US is calculated as $120,000 as of 2008. This is equivalent to approximately €76,500 (using 2008 exchange rates). This calculation is based on dividing the Value of a Statistical Life (VSL) by the number of DALYs corresponding to a premature death. A study by Highfill and Bernstein (2014)[156] values a DALY averted as the value of a year of life in full health and sets this as being in the range of $100,000 to $200,000. This is equivalent to a range between €63,500 and €127,000. However, the study recommends the use of the lower estimate.

DALYs per case

One DALY can be thought of as on lost year of "healthy" life. So, the sum of the DALYs for all incident cases can be thought of as the burden of as the intangible burden of ill-health, as a result of the reproductive effects of the substances studied, compared with a population not exposed.

DALYs for a disease or health condition are calculated as the sum of the years of life lost (YLL) due to premature mortality and the years lost due to disability (YLD):

$$DALY = YLL + YLD$$

YLL can be calculated using the standard life expectancy minus the average life expectancy for a given health effect.

The YLD is calculated as follows:

$$YLD = I \times DW \times L$$

Where:

I = number of incident cases

DW = disability weight

L = average duration of disease

A disability weight is a weight-factor that reflects the severity of the disease on a scale of 0 (perfect health) to 1 (equivalent to death). It represents the intangible costs of the ill-health based on value choices by health-care workers.

In order to attribute a value to the burden of ill-health, the DALY per incident case for each health effect, has been calculated, using the following formula, derived from the formulae above:

$$DALY_I = YLL + (DW \times L)$$

[154] Stassen et al. (2015): DALYs versus WTP for Environmental Health Priority Setting based on Data of Air Pollution and Noise in Flanders. Available at: https://lirias.kuleuven.be/handle/123456789/407179

[155] http://www.popstoolkit.com/economic/training/overview/benefit+quantification/daly.aspx

[156] Highfill and Bernstein (2014): Using Disability Adjusted Life Years to Value the Treatment of Thirty Chronic Conditions in the U.S. from 1987-2010. Available at: https://www.bea.gov/papers/pdf/highfill_bernstein_2014_dalysall.pdf

Therefore, to estimate the DALYs lost per case for each health effect, the following parameters were required:

- Disability weights (DW), including by severity of disease;
- Average duration of disease/health effect (L); and
- Years of life lost (YLL) for a specific disease/health effect.

In addition to these parameters, the following factors need to be considered:

- Whether the effect impacts on the worker or their offspring;
- Whether the effect is linked to male or female/maternal exposures; and
- Assumptions on the percentage of cases linked to different severities of effect, where these are low, moderate or high.

A summary of these parameters, the rationale for their use and the reference source are summarised in Table X1-2.

Table X1-2: Parameters required for estimating DALYs lost per case

Parameter	Rationale	Reference/source
Disability weights (DW)	As explained in the text, disability weights were taken from the European Burden of Disease (EBD) study where possible	European Burden of Disease (EBD) Study
Average duration of health effect (L)	This was estimated	Review of the scientific and health literature
Years of life lost (YLL)	This is calculated, where relevant, based on average life expectancy minus estimated life expectancy with a specific health condition.	Review of the scientific and health literature
Proportion of cases of different severity	The severity of disease dictates the DW, but was not always stratified in the outcome data, therefore average distribution, according to severity is used to calculate a weighted DW	NHS Reference costs 2016/2017

NHS Reference costs 16/17. NHS Reference costs 16/17 https://improvement.nhs.uk/resources/reference-costs/
EBD Study. https://ecdc.europa.eu/sites/portal/files/documents/Haagsma-PopHealthMetrics-2014-Disability-weights.pdf

In some instances, the proportion of cases by severity was required, for example where health effect was reported in studies as spontaneous abortion/still birth. When valuing the health burden, it is necessary to distinguish between the two, as still birth is going to have a greater impact on the individual than spontaneous abortion, resulting in higher DALY values and higher direct and indirect costs. Furthermore, whether a spontaneous abortion required intervention or not, will also have an impact on costs. A search of the health literature gives average proportion of such events and is are summarised in Table X1-3.

Table X1-3: Proportion of events by severity		
Health effect	**Proportion**	**Reference**
Spontaneous abortion/still birth		
Spontaneous abortion	98.7%	Tommys.org (2018)
Still birth	1.3%	
Severity of spontaneous abortion		
Requiring intervention	2.9%	NHS Reference costs 2016/2017
Not requiring intervention	97.1%	
Skeletal effects / limb abnormalities		
Mild	0.400	Estimate
Moderate	0.400	
Severe	0.200	
Tommy's.org (2018) https://www.tommys.org/our-organisation/charity-research/pregnancy-statistics NHS (2017) https://improvement.nhs.uk/resources/reference-costs/		

Because of its European scope and importance, the starting point for the identification of disability weights for use here was the European Burden of Disease (EBD) study[157]; in some cases, where relevant disability weights were not available from the EBD, they were available from the series of studies linked to the World Health Organisations (WHO's) Global Burden of Disease estimates[158]. Thus, for those effects lacking disability weights from the EBD, uncertainty may be introduced by drawing on weights that reflect a global population. It is of note, however, that there is good correlation between the EBD and GBD disability weights across those health outcomes for which both sets of estimates exist. In a few cases, the broader health economics literature was used to fill gaps

The disability weights identified through this combined approach are presented in the table overleaf by category and type of health effect, along with estimated years of lived with disability and years of life lost. As can be seen from this table, disability weights and hence DALYs have only been calculated for a sub-set of the health effects listed in the previous tables, due to a lack of available data and the fact that the full range of effects was not identified for the selected substances.

[157] https://ecdc.europa.eu/sites/portal/files/documents/Haagsma-PopHealthMetrics-2014-Disability-weights.pdf

[158] https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(15)00069-8/fulltext

Table X1-4: Present value of expected (severity weighted) number of DALYs per case (discounted @4%, years 1 to 80)									
Health effect	**Individual impacted and link to exposures**		**Severity frequency**	**DALYs**			**Present value of DALYs lost (Euro, 2016)**		
	Worker or offspring	Effect passed by Male/ Female	% by severity (mild, mod, severe)	Disability weights (DW)	Years lived with disability (L)	Years life lost (YLL)	Total discounted DALYs per severity case	Weighted, discounted DALYs per case	Present value Expected/average DALYs per case
Impaired or reduced fertility female	Worker	F	100%	0.008	1	0	0.008	0.008	800
Impaired fertility - male	Worker	M	100%	0.008	1	0	0.008	0.008	800
Spontaneous abortion	Worker	F	100%	0.114	1	0	0.114	0.114	11,400
Still birth	Worker	F	100%	0.114	5	0	0.528	0.528	52,800
Low birth weight: normal–low	Offspring	F	100%	0.011	80	0	0.257	0.257	25,734
Low birth weight: low–very low			100%	0.185	70	10	4.849	4.849	484,886
Low birth weight: very low–extremely low			100%	0.421	40	40	12.455	12.455	1,245,538
Impaired cognitive development – per IQ point	Offspring	F	-	-	-	-	-	-	9,600
Skeletal effects or abnormalities of the limbs	Offspring	F	40%	0.028	80	0	0.670	6.425	642,477
			40%	0.317	80	0	7.581		
			20%	0.581	40	40	15.622		
Pre-eclampsia	Worker	F	100%	0.324	1	0	0.324	0.324	465,199
	Offspring	F	100%	0.185	70	10	4.328	4.328	
https://ecdc.europa.eu/sites/portal/files/documents/Haagsma-PopHealthMetrics-2014-Disability-weights.pdf *https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(15)00069-8/fulltext*									

Willingness to pay (WTP) values

An alternative method of valuing the intangible costs of ill-health is through willingness to pay (WTP) valuations. Preference is given here to those developed for use by ECHA in Restriction and Authorisation decision making, before drawing from the wider literature. These valuations are either per child/worker affected or per lifetime of effects. As can be seen from Table X1-5 below, there are some significant variations in the valuations, especially from the study undertaken for ECHA in relation to minor birth defects, external birth defects and internal birth defects. ECHA's Socio-Economic Analysis Committee (SEAC) has highlighted the uncertainty that surrounds these estimates due to the fact that they stem from one of the first studies aimed at eliciting people's willingness to pay to avoid reproductive toxicity effects.

In this study, preference is given to DALY values. As a result, the WTP values are not combined with the DALY values. Instead, the WTP values are only used for assessment under the top down approach, where it was not feasible to also identify DALYs for all of the potential developmental effects under consideration.

Resource use and costs per case

These DALY based valuations do not provide a full cost-of-illness based estimate of the economic damage costs associated with the different health effects. In particular, they do not take into account the direct costs of medical treatment, costs of visiting doctors, lost output, etc. Instead, they provide an alternative measure of the "intangible" effects of an illness or disease on an individual's health.

The cost-of-illness approach includes the valuation of:

- Healthcare costs of medical interventions and on-going in-patient and out-patient care
- Healthcare costs of on-going in-patient, e.g. bed stays in hospital, and out-patient care over the life of the individual, e.g. routine follow-up appointments, medication.
- Lost out-put to the individual, including carers of affected children/infants
- Lost out-put to employers from absenteeism, e.g. while workers are undergoing fertility treatment.

Key data sources include health care service provider registries of the costs of different surgical and other interventions. A key issue with these is the significant differences in reporting on costs between Member States, as well as linking interventions to specific types of health effects. For example, the costs of Assisted Reproductive Techniques (ART) quoted in the literature can vary from €6,000 per treatment to over €50,000 per treatment, depending on the actual treatment and the number of cycles.

Similarly, estimates of lost production given in the literature are sometimes quoted as present value figures, with inadequate information given on the discount rate and the period over which costs are assumed to arise. As a result, work is required to generate consistently derived figures for this study. In other cases, there are no studies providing a basis for determining the number of days lost due to a health effect, hospital or doctor visits, care provision, etc.

Table X1-5: Willingness to pay valuations for the human/intangible impacts from different reprotoxic effects			
Health effect	**WTP / Stated preferences valuations**	**Converted to 2018 prices**	**Reference**
Perinatal, late neonatal and infant death	Loss of a child: €4.6 million	€4.9 million	https://www.epa.gov/environmental-economics/seminar-vsl-children-and-adults-evidence-conjoint-choice-experiments-milan Alberini A & Scasny M (2011): Context and the VSL: Evidence from a Stated Preference Study in Italy and the Czech Republic, Environmental and Resource Economics, 49:4, pp 511-538
	€3.5 to 5.0 million for premature death (2012 prices)	€ 3.7 to 5.3 million	ECHA (2017): 32nd Meeting of the Committee for Socio-Economic Analysis, 6-15 September 2016, Helsinki, Finland. SEAC/32/2016/05.1 Rev1+
Embryonic/ foetal development/ Low birth weight / reduced foetal growth	€126,000 (2012 prices) per child as a one-off payment; reflects very low birth weight so may over estimate for less severe cases	€ 134,049	ECHA (2017): 32nd Meeting of the Committee for Socio-Economic Analysis, 6-15 September 2016, Helsinki, Finland. SEAC/32/2016/05.2 Rev1+
Impaired male fertility	€22,000 (2012 prices)	€ 23,405	ECHA (2017): 32nd Meeting of the Committee for Socio-Economic Analysis, 6-15 September 2016, Helsinki, Finland. SEAC/32/2016/05.2 Rev1+
Impaired female fertility	€22,000 (2012 prices)	€ 23,405	ECHA (2017): 32nd Meeting of the Committee for Socio-Economic Analysis, 6-15 September 2016, Helsinki, Finland. SEAC/32/2016/05.2 Rev1+
Impaired fertility – male offspring[1]	€6,700 (2012 prices)	€ 7,128	ECHA (2017): 32nd Meeting of the Committee for Socio-Economic Analysis, 6-15 September 2016, Helsinki, Finland. SEAC/32/2016/05.2 Rev1+
Impaired fertility – female offspring[1]	€6,700 (2012 prices)	€ 7,128	ECHA (2017): 32nd Meeting of the Committee for Socio-Economic Analysis, 6-15 September 2016, Helsinki, Finland. SEAC/32/2016/05.2 Rev1+
Impaired cognitive development – IQ	€9600 per IQ point over the lifetime of the child (2015 prices) – indirect losses in income due to assumed reduced productivity over the lifetime	€ 9,882	Rijk, I et al (2016): Health cost that may be associated with Endocrine Disrupting Chemicals, Institute for Risk Assessment Sciences, University of Utrecht

Table X1-5: Willingness to pay valuations for the human/intangible impacts from different reprotoxic effects			
Health effect	**WTP / Stated preferences valuations**	**Converted to 2018 prices**	**Reference**
Developmental abnormalities: skeletal effects or abnormalities of the limbs	Minor birth defect: €4,300 (2012 prices) Internal birth defect: €128,000 (2012 prices) External birth defect: €26,000 (2012 prices)	€ 4,575 € 136,177 € 27,661	ECHA (2017): 32nd Meeting of the Committee for Socio-Economic Analysis, 6-15 September 2016, Helsinki, Finland. SEAC/32/2016/05.2 Rev1+
Microphthalmia	Internal birth defect: €128,000 (2012 prices)	€ 136,177	ECHA (2017): 32nd Meeting of the Committee for Socio-Economic Analysis, 6-15 September 2016, Helsinki, Finland. SEAC/32/2016/05.2 Rev1+

A pragmatic search of the literature was therefore undertaken to find as many direct and indirect costs relating to the relevant health effects as possible, within the time constraints. Where direct and indirect costs were quoted separately, a value was included for both, where possible. However, in a number of cases direct and indirect costs were quoted as a single figure, either in an economic analysis' or a systematic review of the literature. If this was the case, these costs were quoted as a single figure. In some cases, it was not possible to accurately estimate an indirect cost, for example for spontaneous abortion, however, given that the figure is likely to be relatively low, it was considered reasonable not to include it in the final calculations. A summary of the identified direct and indirect costs is given in Table X1-6.

Table X1-6: Indirect and direct cost-of-illness data for all relevant endpoints

Description	Direct/ Indirect cost	Cost per case (€)	Proportion by severity	Weighted cost per case (€)	TOTAL cost per case (€)
Infertility – male or female					
Cost, per treated couple, of medically assisted reproductive treatment (irrespective of whether terminated by live birth)[a]	Direct	6,607	1	6,607	7,005
Productivity losses (15.6 days over 18 months) adjusted to 1 year – 2 people[b]	Indirect	398	1	398	
Spontaneous abortion					
Medical cost of spontaneous abortion without intervention[c]	Direct	693	0.971	673	734
Medical cost of spontaneous abortion with intervention[c]	Direct	2,105	0.029	62	
Still birth					
Medical costs of still birth, including investigations into cause of death[d]	Direct	2,223	1	2,223	6,691
Additional direct cost of care in subsequent pregnancies after still birth – high estimate[d]	Direct	1,978	1	1,978	
Productivity losses – year 1 – 50% normal work[d]	Indirect	2,490	1	2,490	
Low birth weight					
Paediatric Faltering Growth (Failure to Thrive) with CC Score 0[c]	Direct	1,112	1	1,112	1,112
Paediatric Faltering Growth (Failure to Thrive) with CC Score 1[c]	Direct	1,438	1	1,438	1,438
Cost of VLBW babies for first 18 months of life (Societal - direct (above))[e]	Direct & Indirect	30,230	1	30,230	30,230
Skeletal effects/abnormalities of limbs					
Total life-time costs for patients with spina bifida (inc. indirect costs and increased morbidity[f]	Direct & indirect	528,425	1	528,425	528,425
Pre-eclampsia					
Mean cost per woman of pre-eclampsia with expectant management (Euros, 2007). This includes direct medical costs, indirect costs to patients (travel and informal care), and productivity loss[g]	Direct & indirect	7,908	1	7,908	7,908
Impaired cognitive development					
Impaired cognitive development – per IQ point	Direct & indirect	9,600	1	9,600	9,600

[a]Christiansen *et al.* (2014) *Acta Obs Gyn Scand* 93;64–72; [b]Wu A *et al.* (2013) *Fertility and Sterility* 99;2025–30; [c]*NHS Reference costs (2017)* https://improvement.nhs.uk/resources/reference-costs/; [d]Heazzell *et al.* (2016) *Lancet* 387;604–16; [e]Cavallo M *et al.* (2015) *Italian J Paediatrics* 41;59; [f]Yi Y *et al.* (2011) *Eur J Paediatr;* 170;1391–400; [g]VIjgen SMC *et al.* (2010) *BJOG* 117;1577–85.

As impaired cognitive development was measured by the number of IQ points lost, rather than the number cases, a cost (€) per IQ point lost was used. This figure is taken from previous restriction dossiers, which reviewed the literature and established that a 1-point increase (decrease) in IQ leads to and increase (decrease) in lifetime productivity of 0.3–1.5%, with a central estimated of 1%. In combination with lifetime labour market earnings, the benefit (cost) per IQ-point gained (lost) is around €9,600.

Annex 2 Summary of the Consultation Exercise (Round 1)

X2.1 Introduction

The aim of the **first phase** consultation was to collect data on the current exposure to reprotoxic substances in the workplace, risk management measures (RMMs) that are in place, and relevant national legislation. This will allow a more nuanced understanding of the various factors affecting levels of exposure, as well as a better understanding of the various uses and processes during which exposure to the substances in question can occur.

This section summarises the state of the consultation exercise. Please note that a deadline extension has been provided to some stakeholders and it is expected that the study team will receive additional responses.

Stakeholders were initially contacted via email with an overview of the study and a link to the holding page on the RPA website for the study[159], which had links to the online questionnaires in various languages. If the stakeholders preferred to answer in a Word document (i.e. so that multiple colleagues could feed into the response), that was also an option.

In total, 705 stakeholders across the EU-28 were contacted. This figure can be broken down into four groups: national authorities, associations (both EU and national level), OSH practitioners, and trade unions. Companies were invited either directly or through their associations.

Stakeholders were asked to reply through a questionnaire, which was the primary method of data collection in this phase. There were five different questionnaires, for the following stakeholder groups:

- National authorities
- Industry Associations
- Companies
- OSH practitioners and other stakeholders
- Trade unions

The breakdown can be seen in the summary table below.

Table X2-1: Summary of numbers of stakeholders contacted and outcomes

Stakeholder type	Total number of people contacted	Total organisations contacted
National authorities	126	80
Associations	302	293
Companies	N/A (Contacted through associations)	N/A (Contacted through associations)
OSH practitioners	68	57
Trade Unions	209	174
Total	**705**	**604**

All questionnaires were made available on our online portal in the following languages:

- English

[159] See http://rpaltd.co.uk/reprotoxic-substances-consultation

- Spanish
- German
- French[160]
- Polish

At the end of the questionnaire, respondents were offered the chance to provide their contact details, and consent to a potential follow-up interview clarifying their responses (if necessary), and/or asking further questions based on information discovered in other questionnaires.

X2.2 Responses by stakeholder type

112 responses have been received to date and approximately 10 are still expected (participants who required more time to complete their response). The next table provides the breakdown of respondents.

Table X2-2: Breakdown of questionnaire responses per stakeholder type	
Stakeholder type	**Questionnaire responses**
National authorities	27
Associations	13
Companies	45
OSH practitioners	11
Trade Unions	25
Total	**121**

To calculate the response rate, the number of organisations contacted was used instead of the number of stakeholders, as it is unlikely two stakeholders from the same organisation would reply. For example, 80 national authorities (I.e. health and safety executives, ministries who control relevant policy etc.) were contacted, but 126 individuals at said authorities were contacted. The percentages can be seen in the table below.

Table X2-3: Percentage of organisations contacted who replied	
Stakeholder type	**Response rate**
National authorities	34%
Associations	4%
Companies	N/A
OSH practitioners	19%
Trade Unions	14%
Average	**20%**

As can be noted from the above table, the response rate for national authorities is substantially higher than it is for other stakeholder types. It is thought this was because as the legislative bodies for their respective Member States, the onus would be on them more than other stakeholders to offer explanations of the potential effects of changing legislation on reprotoxins. The response rate for associations is particularly low because many associations who were contacted did not have members who used reprotoxic substances or have experience/knowledge themselves of such chemical agents,

[160] French translations were provided with the exception of the national authority questionnaire. French authorities were contacted directly by an RPA associate based in Paris.

and thus, the study was not of relevance; although it should be noted that key associations have provided input. Many associations also simply passed the companies questionnaire onto their member companies.

The study team also received 11 further responses from Member State authorities (CY, DE, DK, EE, ES, FI, FR, LT, LU, LV, SE) which answered follow up questions said authorities were asked where their answers were not necessarily clear and needed further clarification. In addition, these follow-ups also included questions on accidental exposure, personal protective equipment (PPE) and personal hygiene requirements related to reproductive toxins.

X2.3 Responses by chemical agent

The following table provides a breakdown of the questionnaire responses per chemical agent.

Table X2-4: Breakdown of questionnaire responses per chemical agent	
Chemical agent	**Number of questionnaire responses**
4,4'-isopropylidenediphenol (Bisphenol A, BPA) (EC No: 201-245-8; CAS No: 80-05-7)	4
Dinoseb (EC No: 201-861-7; CAS No: 96-45-7)	0
Imidazolidine-2-thione (EC No: 202-506-9; CAS No: 6945-7)	1
4-tert-butylbenzoic acid (EC 202-696-3; CAS No: 98-73-7)	1
2-ethyoxyethanol (EC No: 203-804-1; CAS No: 110-80-5)	2
2-(4-tert-butylbenzyl)propinolaldehyde (EC No: 201-289-8; CAS No: 80-54-6)	0
Borates	9
Tin	2
Dodecyl	0
Retinol	1
Lead compounds	6
Other Cat. 1A/1B reprotoxin(s)	19
General response (not specific to any one chemical agent)	13

As the above table shows, not every response provided detailed information on a chemical agent. There were no questionnaire responses specifically discussing dinoseb, 2-(4-tert-butylbenzyl)propinolaldehyde and dodecyl, whilst borates and lead received a significant number of responses.

The table below details the breakdown of answers for certain substance groups. As it shows, all nine borates-related responses at least referred to boric acid, and seven also referred to disodium tetraborate, anhydrous, which would indicate legislative changes to these two chemical agents are of primary concern to the industry. There were fewer responses regarding tin and retinol.

Table X2-5: Breakdown of questionnaire responses per chemical agent	
Chemical agent	**Number of questionnaire responses**
Borates - Diboron trioxide (EC No: 215-125-8; CAS 1303-86-2)	3
Borates - Disodium tetraborate, anhydrous (EC No: 215-540-4; CAS No: 1303-96-4, 1330-43-4, 12179-04-3)	7
Borates - Boric acid (EC No: 233-139-2; CAS No: 10043-35-3	9
Borates - Disodium octaborane (EC No: 234-5541-0; CAS 12008-41-2, 12280-03-4)	4

Table X2-5: Breakdown of questionnaire responses per chemical agent	
Chemical agent	**Number of questionnaire responses**
Tin - Dibutyltin dilaurate (EC No: 201-861-7; CAS No: 77-58-7)	1
Retinol - Retinol (EC No: 200-683-7; CAS No: 68-26-8)	1
Lead compounds - Lead (EC No: 231-100-4; CAS No: 7439-92-1)	4
Lead compounds - Lead di(acetate) (EC No 206-104-4; CAS No: 301-04-2, 6080-56-4)	2
Lead compounds - Trilead dioxide phosphonate (EC No: 235-252-2; CAS No: 12141-20-7)	1

X2.4 Responses by enterprise size

Many respondents answering on behalf of a company skipped the question on enterprise size. As the below table shows, a majority of respondents who did answer were SMEs – 18, or 64%. The split between small, medium and large enterprises is fairly balanced (and one should bear in mind that, typically, it is larger companies who respond, due to having more resources and thus being able to dedicate staff and time to filling out a questionnaire).

Table X2-6: Breakdown of questionnaire responses by company size	
Company size	**Number of questionnaire responses**
Micro enterprise (less than 10 persons employed)	1 (2.4%)
Small enterprise (10-49 persons employed)	9 (21.4%)
Medium-sized enterprise (50-249 persons employed)	9 (21.4%)
Large enterprise (250 or more persons employed)	19 (45.2%)
No response	4 (9.5%)
Total	**42 (100%)**

X2.5 Responses by Member State

The breakdown of responses by Member State is provided below.

Table X2-7: Breakdown of questionnaire responses by member state					
Member State	**Number of responses per questionnaire type**				
	Companies	**Industry associations**	**National authorities**	**OSH practitioners**	**Trade Unions**
Austria			2	2	1
Belgium	1		1		
Bulgaria			1		2
Croatia	7				1
Cyprus			1		1
Czechia					
Denmark	1		1	1	1
Estonia			1		
Finland	1		1	1	2
France	4	1	1		1
Germany	6	4	3	2	1
Greece			1		
Hungary	1				

Table X2-7: Breakdown of questionnaire responses by member state					
Member State	Number of responses per questionnaire type				
	Companies	Industry associations	National authorities	OSH practitioners	Trade Unions
Ireland			1		1
Italy	15	1	2	1	3
Latvia			1		
Lithuania			2		
Luxembourg	1				
Malta			1		2
Netherlands	1				
Poland			2	1	
Portugal					
Romania			1		1
Slovakia					
Slovenia			1		1
Spain	2	2	1		
Sweden	2		1		
UK	3		1	1	1
EU-wide		5		1	5
Non-EU				1 (Switzerland)	1 (Norway)
Total	**45**	**13**	**27**	**11**	**25**
Overall total	**121**				

X2.6 Policy scenario for changes of CAD and CMD

All stakeholders were asked if they believe there is a need for modernisation of some aspects of the CAD and CMD, for example, to improve their practical implementation. Their responses are summarized in the table that follows:

Table X2-8: Stakeholders believing that some aspects of CAD & CMD require modernisation					
Response	No. of companies	No. of Industry Associations	No. of Trade Unions	No. of Experts	No. of National Authorities
Yes	8	10	18	9	17
No	3	3	0	1	5
Do not know	14	2	3	1	7
No response	17	5	2	4	1
Total	**42**	**20**	**23**	**15**	**30**

The majority of industry associations, trade unions, experts and national authorities believe that some aspects of CAD and CMD require some improvements. In general, it is estimated that CAD and CMD require modernisation in the following aspects: terminology, scope, risk assessment, accidents, incidents, emergencies (unforeseen exposure), information and training, health surveillance, hygiene and individual protection, prohibited activities, exposure and/or biological limits. A significant number of companies, did not respond to this question.

The figure that follows indicates that trade unions are those stakeholders that consider these changes as essential.

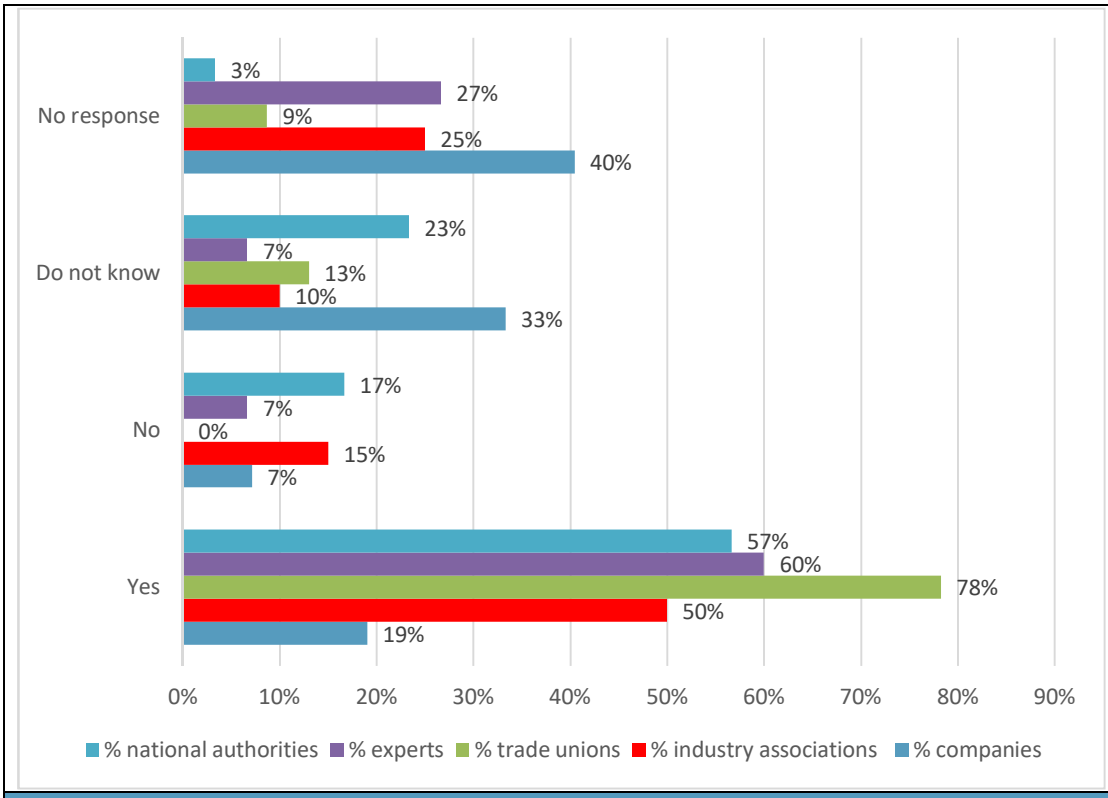

Figure X2-1: Percentages of stakeholders that believing that CAD & CMD require modernisation
Consultation Round 1 questionnaire – All stakeholders

X2.7 Policy option for CMD

National authorities, trade unions, industry associations and OSH experts were asked if they believe that Reprotoxic 1A/1B substances should be included into the scope of the CMD. Their responses are summarised in the following table. As it can be seen from the table, the majority of national authorities and trade unions has responded positively. However, a considerable proportion of industry associations and OSH experts believe that that this change should not occur. The large numbers of non-responses and 'do not know' for these two types of stakeholders suggests uncertainty.

Table X2-9: Stakeholders believing R 1A/1B substances should be included into the scope of the CMD

Response	% of all National Authorities	% of all Trade Unions	% of all Industry Associations	% of all Experts
Yes	63%	74%	5%	27%
No	17%	0%	40%	40%
Do not know	13%	13%	25%	7%
No response	7%	13%	30%	27%
Total	**100%**	**100%**	**100%**	**100%**

X2.8 Policy option for BLVs and BGVs under the CMD

Companies, industry associations, national authorities and OSH experts were also asked if it would be useful to have the option of introducing Biological Limit Values (BVLs) or Biological Guidance Values (BGVs) under the CMD. Their responses are summarised in the following graph.

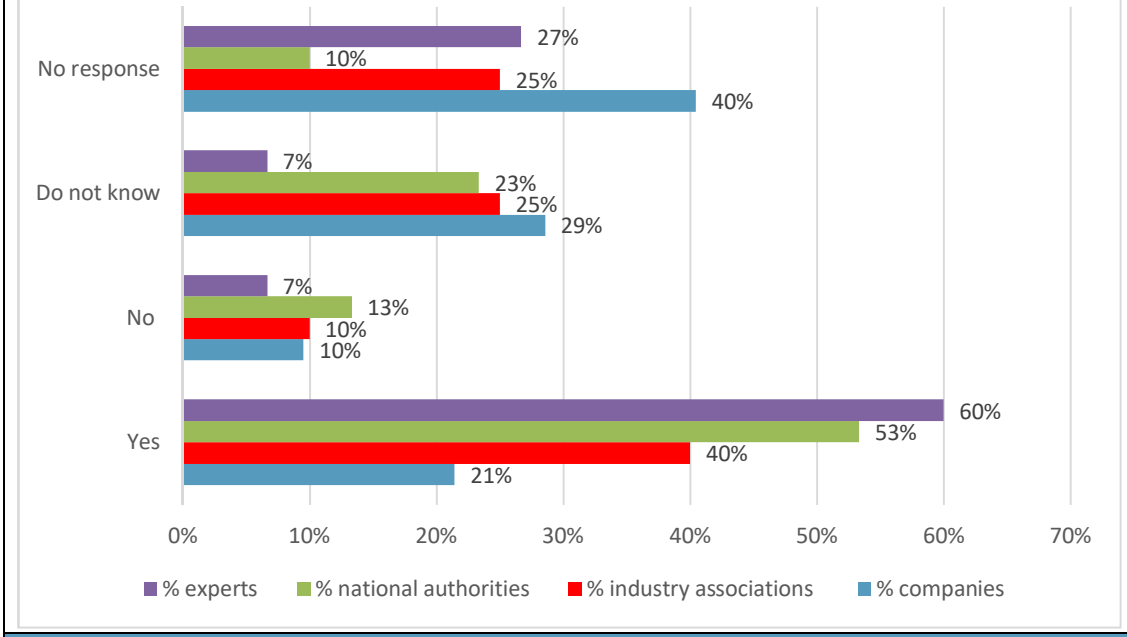

Figure X2-2: Percentages of stakeholders believing that introducing BLVs or BGVs under the CMD would be a useful policy option
Consultation Round 1 questionnaire – All stakeholders, excluding trade unions

The large percentages of companies that did not respond or responded 'Do not know' indicate the uncertainty of this type of stakeholders. Contrary to this, significant percentages of OSH experts and national authorities responded positively.

X2.9 Exposure to reprotoxic substances

Companies, national authorities, experts and trade unions were asked to indicate whether they expect the number of exposed workers or the extent of exposure (duration, frequency, level of exposure) to the relevant reprotoxic substance(s) to change in the future. The results of their responses can be summarized in the following graph.

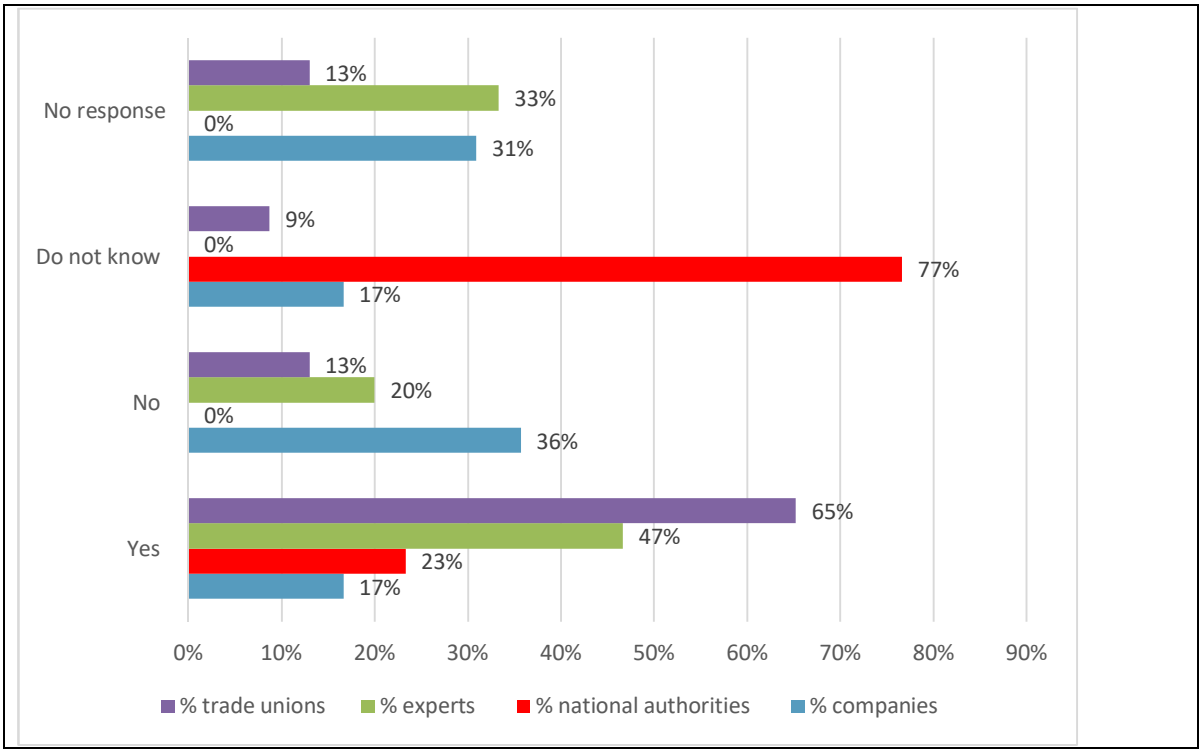

Figure X2-3: Percentages of stakeholders believing the number of exposed workers is likely to change in the future
Consultation Round 1 questionnaire – All stakeholders, excluding Industry Associations

OSH experts and trade unions are these stakeholders expecting the number of exposed workers and the level of exposure to change in the future, while there is uncertainty on this aspect for national authorities. Contrary to this, the split between the responses is balanced for the companies, with 36% of them indicating that they do not expect such a change to occur in the future.

X2.10 Biological monitoring

Companies and OSH experts were asked whether biological monitoring is carried out for the relevant reprotoxic substances and the results are summarized in the table below.

Table X2-10: Stakeholders that have carried out biological monitoring for reprotoxic substances

Response	% of all companies	% of all OSH experts
Yes	24%	47%
No	36%	20%
Do not know	2%	0%
No response	38%	33%
Total	100%	100%

X2.11 Air measurements in the workplace

Companies and OSH experts were also asked whether workplace air measurements of the relevant reprotoxic substances are carried out. The responses are summarised in the following graph.

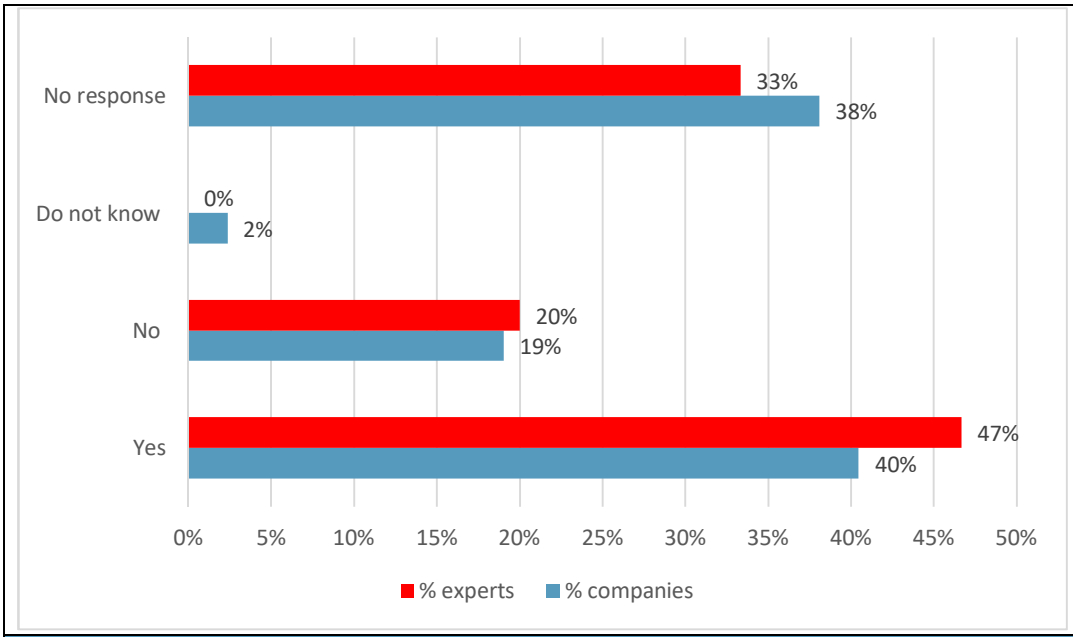

Figure X2-4: Percentages of stakeholders that carry out workplace air measurements of the relevant reprotoxic substances
Consultation Round 1 questionnaire – Companies and OSH experts included

The percentages of those stakeholders that responded positively are larger than those indicating that they do not carry out air measurements in their workplace and larger than those that expressed uncertainty.

X2.12 Conclusion

A significant amount of information was collected through our consultation's questionnaires. Efforts were made to contact a variety of stakeholders in each stakeholder group.

It is important to note that certain chemical agents received substantially more questionnaire replies than others, which could potentially be indicative of the perceived importance of said agents. For example, the lack of response regarding dinoseb is likely to be a result of its use/application being banned in the EU.

The below table offers a summary of the activities undertaken during the first phase of consultation.

Table X2-11: Breakdown of stakeholders contacted, organisations contacted, and questionnaires received				
Stakeholder type	**Stakeholders contacted**	**Organisations contacted**	**Questionnaire responses**	**Response rate (%)**
National authorities	126	80	27	34%
Associations	302	293	13	4%
Companies	N/A (Contacted through associations)	N/A	45	N/A
OSH practitioners	68	57	11	19%
Trade Unions	209	174	25	14%
Total	**705**	**604**	**121**	**20%**

Annex 3 Further Information on Legislation in EU and non-EU countries

X3.1 Introduction

This section summarises the key features of the existing regulatory approaches within the EU and in key non-EU countries.

This includes a review of the regulatory systems seeking to protect workers from risks arising from occupational exposure to Repro. 1A and 1B substances at the EU level, in EU Member States, non-EU EEA Countries (Norway, Iceland and Liechtenstein) and major EU trading partners.

This section is structured as follows:

- Description of the EU regulatory system;
- Review of existing national legislation (EU and non-EU countries);
- Identification and review of proposals to change legislation; and
- Synthesis of findings.

Further information is provided in Annex 3, which summarises the provisions that EU Member States have adopted in their national legislation transposing the CAD and CMD and which go beyond the minimum requirements in the CAD and CMD with regard to risk assessment, risk management, and other measures. The annex also summarises the legal approaches to the regulation of reprotoxic substances in EU and non-EU countries.

X3.2 Description of the EU regulatory system

X3.2.1 Description of the overall legal framework

In the EU, the safety of chemicals at the workplace is regulated by legal instruments adopted within the EU Occupational Safety and Health (OSH) legal framework, as well as under the EU chemical policy framework where legislation seeks to protect human health and the environment more generally.

The overarching EU legislation governing OSH is Directive 89/391/EEC (the Framework Directive) on the introduction of measures to encourage improvements in the safety and health of workers at work. As a framework Directive, 23 subsequent Directives have been introduced for specific matters. The four Directives which are most relevant to reprotoxic substances are:

- The Chemical Agents Directive 98/24/EC (the CAD);
- The Carcinogens and Mutagens Directive 2004/37/EC (the CMD);
- The Pregnant Workers Directive 92/85/EC (the PWD);
- The Young Persons at Work Directive 94/33/EEC (the YPWD).

Among the broader measures of the EU chemicals policy, the main legislation includes:

- The REACH Regulation (EC) No 1907/2006 (the REACH Regulation or REACH), and
- The CLP Regulation (EC) No 1272/2008 (the CLP Regulation or the CLP)

REACH and the CLP cover all chemicals and seek to protect human health and the environment. In doing so, they also contribute to the overall protection of workers from risks to their health arising from occupational exposure to chemicals.

X3.2.2 Key features of the OSH & chemicals legal frameworks

Directives vs Regulations

The OSH framework relies on directives adopted pursuant to Article 153 of the TFEU, which impose minimum OSH requirements. Consequently, EU Member States must transpose such Directives and may adopt more stringent measures when doing so.

By contrast, the chemicals policy framework, relies on regulations to achieve the protection of human health and the environment as well as the free circulation of chemical substances within the internal market. The relevant regulations have been adopted pursuant to Articles 191 to 193 of the TFEU and are directly applicable in the Member States.

Coexistence of the two frameworks

REACH applies "without prejudice to Community workplace and environment legislation" (REACH Recital (5)), including the Framework Directive 89/391/EEC, and thus the CAD and the CMD as well (Article 2.4 of REACH).

Whilst there are not many specific provisions seeking to ensure workers' protection within REACH and the CLP, there is no doubt that these regulations, when seeking to protect human health, also seek to protect workers. For example, REACH Recital 7 provides that "to preserve the integrity of the internal market and to ensure a high level of protection for human health, especially the health of workers, and the environment, it is necessary to ensure that manufacturing of substances in the Community complies with Community law, even if those substances are exported".

In addition, REACH also includes a specific provision related to access to information for workers (Article 35) that requires them and their representatives to be granted access by the employer to the information that is to be made available in the supply chain (mainly Safety Data Sheets) in relation to the substances and preparations that they use or may be exposed to in the course of their work.

Regulatory coverage of CM vs R substances

All classified substances fall under the scope of the CAD, but only carcinogens and mutagens of categories 1A/1B (C/M 1A/1B) are subject to the CMD. The reasons for this include the fact that carcinogens and mutagens can have severe health impacts, and the fact that at the time of adoption of the CAD, scientific knowledge did not allow the setting of a threshold below which carcinogens and mutagens presented no risk. Hence, the legislator sought to control the occupational exposure to C/M 1A/1B substances using an additional legal instrument.

Reprotoxic substances are only subject to the CAD, unless they are also classified as C/M 1A/1B, in which case they fall within the scope of the CMD as well. It should be noted that a significant number of substances with a harmonised classification of reprotoxic 1A/1B (R 1A/1B) are not classified as carcinogenic or mutagenic. Additionally, many substances do not have a harmonised classification under the CLP but have been self-classified as being reprotoxic under the CLP.

By contrast, REACH and the CLP contain specific provisions dealing with CMR substances together, without distinguishing between CM and R (e.g. Article 57 REACH on Substances of Very High Concern).

- CMR 1A/1B have been prioritized for registration by the first registration deadline of 1 June 2010 if manufactured or imported above 1 ton per year per manufacturer or importer (REACH Article 23.1(a)).
- CMR 1A/1B are among the classification criteria triggering the qualification as 'substances of very high concern' under REACH (Article 57) and their possible listing in the 'Candidate List' (Article 59) and eventually in Annex XIV (Article 58) for being subject to the REACH authorization process.
- CMR 1A/1B are also subject to specific classification rules under the CLP and only information on CMR substances can be used to classify mixtures containing them (Article 6.3).
- Various restrictions apply to CMR 1A/1B with regard to their manufacturing, placing on the market and use, as established under Annex XVII of REACH.

Additionally, there are numerous legislative acts covering downstream uses which regulate CMR 1A, 1B and 2 substances, that do not distinguish between CM and R either, such as the Cosmetic Regulation 1223/2009 and the EU Biocides Regulation 528/2012, to name just a few.

Assessing effective control of exposure to Chemicals in the workplace[161]

In order to ensure safe conditions, either for using chemicals in the context of REACH, or with regard to working conditions in the case of the CAD or CMD, the regulations mandate the use of tools that define exposure limits for humans. On the one hand, the CAD and the CMD prescribe Occupational Exposure Limits (OELS), referring to the airborne concentration of harmful chemical agents. On the other hand, under REACH, Derived No Effect Levels (DNELs) must be adopted are refer to the levels of exposure to a substance above which humans should not be exposure. While the values are used to characterise the risk and determine potential risk management measures (RMM), there are key differences among the two.

OELs are established at EU and national level, generally supported by expert independent scientific committees which consider all available scientific information, and complemented by information on exposure monitoring. Generally, OELs only considered the inhalation route of exposure, although they may indicate that another route of exposure is important. There are two different types of OELs at the EU level. First, Indicative Occupational Exposure Limit Values (IOELVs), which are health-based limits typically established for substances for which it is possible to set a threshold or a no effect level. Prior to adoption of an OEL, the European Commission's Scientific Committee for Occupational Exposure Limits (SCOEL) will perform an assessment of scientific information, taking into account the availability of measurement techniques. Once an OEL has been set at the EU level, Member States will have to introduce a national OEL, that must take into account the EU limit value. The second type of EU level OEL, is Binding Occupational Exposure Limit Values (BOELVS) that take into account socio-economic and technical feasibility factors in addition to the factors considered for IOELVs. These values aim to provide a minimum level of protection for workers at the Community level. Where BOELs exist, Member States will have to establish a national OEL based on, but not exceeding, the EU limit value. Whether an employer will have to comply with national OELs will depend on the legislation of the relevant Member State(s) and compliance with OELs may be monitored by measuring the concentration of the concerned chemical(s) in the air of the work environment.

DNELs are non-binding levels introduced by REACH and formulated by registrants (manufacturers and importers) notably as part of their REACH registration of chemical substances. They are derived for all relevant routes of exposure but only when a chemical safety assessment (CSA) is required, i.e. for

[161] See the Commission's 'Interim Guidance for National Labour Inspectors on how to use Occupational Exposure Limits (OELs), Derived No Effect Levels (DNELs) and Derived Minimal Effect Levels (DMELs) when assessing effective control of exposure to Chemicals in the workplace', SLIC WG CHEMEX, November 2015.

production/import volumes of at least ten tonnes per year. The levels are established according to a methodology set up by ECHA that differs from the methodology used by SCOEL. The CSA and the DNELs will be documented in the Chemical Safety Report (CSR) and the extended Safety Data Sheet (eSDS). Additionally, for chemical substances that do not have a threshold and for which it is therefore impossible to set a DNEL, REACH provides the possibility to set a Derived Minimal Effect Level (DMEL) rather than a DNEL, which is a reference level considered to be of very low concern. In such cases, the conditions in the exposure scenario for safe use are based on a qualitative assessment.

OELs and DNELs or DMELs co-exist and may sometimes apply simultaneously to certain work activities. DNELs are often lower than OELs and although the values are not interchangeable, REACH registrants can use an OEL, where it exists, as a DNEL for the inhalation route. When a DNEL is lower than an OEL, the RMM to meet the DNEL should nevertheless ensure that the OEL is also achieved. If it is the other way around, i.e. the DNEL is higher than the OEL, chemical users subject to OSH legislation, are required to ensure that exposure is controlled below the OEL. Lastly, if both the DNEL and the OEL are the same, provided that the RMM are effective at controlling exposure below the DNEL, they will also control the level below the OEL. However, the RMM that are set out based on the DNEL will not always allow for an employer to fulfil his RMM obligations under the OSH legal framework. Thus, the employer will also have to assess whether the RMM ensure compliance with his OSH duties.

X3.2.3 The CAD and the CMD, within the OSH legal framework[162]

The CAD sets out minimum requirements for the protection of workers from risks to their safety and health arising, or likely to arise, from the effects of chemical agents that are present at the workplace or as a result of any work activity involving chemical agents. Reprotoxic chemicals are covered by the CAD's broad scope of application and can present two groups of effects:

5. Effects on sexual function and fertility; and
6. Effects on the development of the foetus or offspring (developmental toxicity).

Among employer requirements under the CAD, figures the obligation to determine whether any hazardous substances are present at the workplace and assess any risk to the safety and health of workers. This assessment will notably take into account OELs that have been adopted under the CAD and whether such limit values are respected at the workplace. Based on the results of the risk assessment, employers must take any necessary preventive measures and/or eliminate or reduce the risks to a minimum, following a hierarchy of prevention and risk management measures.

The CMD aims to protect workers against health and safety risks from exposure, or likeliness thereof, to carcinogens or mutagens at work but reprotoxins may indirectly fall within the scope of the CMD if

[162] The following report is focused on the regulatory systems that have been put in place within EU Member States while implementing the CAD and CMD in order to protect workers against from risks to their health arising from exposure to reprotoxic chemicals Cat 1A/1B, and the systems that have been set up with the same view in certain non-EU Member States. To that effect, this section does not consider:

- Occupational Exposure Limit Values (OELVs) or Biological Limit Values (BLVs) that are established following the implementation of the CAD and CMD;
- Legislation that may set out the OELVs and BLVs;
- Legislation implementing Directive 92/85/EEC on Pregnant Workers;
- Legislation implementing Directive 94/33/EC on Young People at Work;
- Legislation applicable to specific substances such as lead or asbestos;
- Legislation applicable to types of exposure such as radiation;
- Legislation other than federal where a country is a federal state.

they are also C/M 1A/1B.[163] The CMD requires employers to assess any risk to workers' health or safety and ensure that the binding limit values in Annex III are not exceeded. They must also apply a range of prevention measures whenever carcinogens or mutagens are used as the workplace and replace the substances in so far as technically possible or reduce exposure to as low as level as possible, according to the hierarchy of risk management measures.

Next to the CAD and the CMD, two other Directives regulating reprotoxins were mentioned above. The PWD and YPWD are complementary to the CAD and CMD and aim to protect the health and safety of workers that are at particular risk, at their workplace.

In that respect, the PWD aims to protect women, when pregnant, having recently given birth and/or breastfeeding. The Directive sets out a non-exhaustive list of activities liable to involve a specific risk for such women and that require employers to perform a risk assessment, based on the Guidelines drawn up by the Commission. Where such assessment reveals a risk to the safety or health of the concerned women or an effect on their pregnancy or breastfeeding, employers must take action to avoid the risk. Certain activities are specifically prohibited for such workers. Furthermore, the PWD lays down minimum requirements for maternity leave and employment rights for women that are pregnant, have recently given birth and/or are breastfeeding.

The YPWD, aims to establish minimum requirements for the protection of young people at work, i.e. people under the age of 18. The Directive instructs Member States to take the necessary measures to prohibit work by children and ensure that the minimum employment age is not lower than 15 years old. When young people are at work, their working conditions must be adapted to their age and Member States shall ensure that they are protected from any specific risks to their safety, health and development linked to their age. To that effect, certain categories of work are prohibited to young people, including for example, work involving exposure to CMRs. Further work modalities are specified in the Directive, which also allows Member States to adopt exceptions for specific types of work. The measures set out in the Directive are to be implemented by employers, prior to the young people starting work and on the basis of a comprehensive risk assessment of the hazards to young people due to their work.

X3.2.4 Main Differences between the CAD and the CMD

The key issue for the analysis under this study are the differences between the legal regimes relevant to substances that are only Reprotoxic 1A/1B and are thus only subject to the CAD, and substances that are C/M 1A/1B or both Reprotoxic 1A/1B and C/M 1A/1B and are thus also subject to the CMD. The following table summarizes the provisions of the CAD and the CMD in a comparative way to present the differences between the provisions of both Directives. Based on the observations stemming from the table, this section will then focus on the main elements distinguishing the CAD and the CMD.

Table X3-1: Differences between the CAD and CMD		
Area	**Chemicals at Work Directive (CAD)**	**Carcinogens and Mutagens Directive (CMD)**
General provisions		
Legal basis	Article 16.1 OSH Framework Directive, minimum requirements	Article 16.1 OSH Framework Directive; minimum requirements

[163] See https://osha.europa.eu/en/legislation/directives/directive-2004-37-ec-indicative-occupational-exposure-limit-values

Table X3-1: Differences between the CAD and CMD		
Area	**Chemicals at Work Directive (CAD)**	**Carcinogens and Mutagens Directive (CMD)**
Scope	▪ Hazardous chemicals present or may be present at the work place (Art. 1.2 & 2.(b)) ▪ Reference to the CLP Regulation (Art.1.2 & 2.(b)(i)) ▪ Carcinogens: more stringent requirements in specific legislation prevail (Art.1.3)	▪ Activities where workers are or are likely to be exposed to carcinogens or mutagens (CM) as a result of their work (Art.3.1) ▪ Reference to the CLP Regulation and/or substance, mixture or process (or released by a process) listed Annex I to CMD (Art.2.a)
Employer obligations		
Risk assessment[164]	Determine whether hazardous chemicals are present at the work place (Art.4.1) If yes, perform a risk assessment (Art.4.1)	Determine whether workers are exposed or likely to be exposed to CM as a result of their work (Art.3.1) If yes, perform a risk assessment → determine the exposure & RMM
Prevention/ reduction of occupational risks[165]	If activity involves hazardous chemical agents: General preventive measures or Art. 6(1) and 6(2) of **Dir.89/931** (Art. 5.1) 'Risks' shall be eliminated/reduced to a min. through: • List of General preventive measures in Art. 5.2 (Art. 5.2) If 'slight risk' is identified, because of quantities of chemical present: ▪ General preventive measures of Art. 6(1) and 6(2) of Dir.89/391; ▪ General preventive measures of Art. 5.2 → IF sufficient to reduce risk ➔ No other measures (Art. 5.4) If risk is identified (>'slight risk'): (Art. 5.3) • Comply with hierarchy for further RMM: 3) Substitution of the chemical 4) IF the nature of the activity does not permit risk to be eliminated by substitution: → Reduction of the risk to a min. by applying protection and prevention measures in the following order: – designing processes, controls,	Reduce the use of CM substances at the place of work, in particular by replacing it, IF technically possible (Art.4.1) If replacement not technically impossible: ▪ Comply with hierarchy for RMM: ▪ Closed system; ▪ IF closed system technically impossible: → Reduction of the level of exposure as low as technically possible (Art.5.2&5.3) Wherever a CM is used: Implement mandatory list or general prevention measures (all provided in Art. 5.5) ▪ Limitation of the quantities of CM at the place of work; ▪ Keeping the number of workers exposed/likely to be exposed to as low a level as possible; ▪ Designing processes, controls, using adequate equipment; ▪ Evacuation of CM at source; ▪ Collective protection measures at the source of the risk; ▪ Individual protective measures; ▪ (…)

Table X3-1: Differences between the CAD and CMD		
Area	**Chemicals at Work Directive (CAD)**	**Carcinogens and Mutagens Directive (CMD)**
	using adequate equipment; – collective protection measures at the source of the risk; – individual protective measures:(Art.6.2 – 6.6) ▪ Implement provisions to deal with accidents, incidents and emergencies (art.7) ▪ Implement health surveillance measures where appropriate (art.10 & 6.3)	
Accidents, incidents and emergencies **Called 'unforeseen exposure in CMD'**	▪ If risk is identified (>'slight risk'): – Prepare action plans to deal with accidents, incidents and emergencies (Art.7.1) – In the event of accident, incident or emergency: ✓ Mitigate the effects and inform the workers (Art.7.2) ✓ Provide PEE to workers in the affected areas (Art.7.3) ✓ Provide warnings & communicate on the increased risk for health and safety (Art.7.4) Provide information on emergency arrangements: list (Art.7.5)	▪ Inform workers (Art.7.1) Permit access only to workers who are essential to carry the repairs and other necessary work, equipped with PPE (Art.7.2)
Information and training[166]	▪ Provide workers and/or their representatives with relevant training, data and information; list applies in addition to Framework Regulation (Art.8)	▪ Provide workers and/or their representatives with relevant training, data and information; list provided (Art.11&12) ▪ Consultation of workers for the implementation of CMD (Art.13)
Health surveillance (HS)[167]	▪ If risk is identified (>'slight risk'): – Cases where HS is required: based on exposure, likelihood of disease, etc.); compulsory if BVL (Art.10.1) – Techniques for detection of diseases (Art.10.1) – Health and exposure records (Art.10.3) ▪ If disease of a worker information, review safety assessment, search advise, continue HS (Art.10.4)	▪ If risk is identified: – For workers at risk based on the risk assessment → compulsory HS in compliance with national laws (Art.14.1) – Surveillance before and after exposure (Art.14.2) – Health and exposure records (Art.14.4)

Table X3-1: Differences between the CAD and CMD		
Area	**Chemicals at Work Directive (CAD)**	**Carcinogens and Mutagens Directive (CMD)**
		▪ If disease/abnormality of a worker → doctor or other authority may require HS for other workers
Hygiene and individual protection	N/A	Comply with list in Article 10: ensure that no eating, drinking, smoking in C&R areas; protective clothing; storage and washing facilities; etc.
Prohibited activities	Article 9 and Annex III (prohibited substances)	N/A
Occupational limits		
Occupational exposure limits (OEL)	IBOELV: MSs must establish national OEL 'taking into account' the EU value BOELV: MSs must establish corresponding national binding OEL ≤ EU value	▪ Only BOELVs: MS must establish a corresponding national binding OEL ≤ EU value ▪ Requirement that employers comply with such OEL
Biological limit values (BLV)	MSs must establish corresponding national binding BLV ≤ EU value	N/A

Starting points of the Directives

The first major difference between the CAD and the CMD is the starting point of each Directive, the element triggering their application.

According to article 1.2 of the CAD, the requirements set out in this Directive are applicable "where hazardous chemicals are present or may be present at the workplace". This creates a broad scope of application corresponding to the goal of the CAD, laid out in article 1.1, which is "the protection of workers from risks to their safety and health arising, or likely to arise, from the effects of chemical agents present at the workplace or as a result of any work activity involving chemical agents". The CAD specifies in article 1.3 that its provisions are applicable without prejudice to more stringent/specific measures taken under the CMD.

The CMD also aims to "protect workers against risks to their health and safety" under article 1.1 of the Directive. It is further specified that the CMD aims at the "prevention of such risks, arising or likely to arise from exposure to carcinogens or mutagens at work". The requirements of the CMD apply accordingly and will concern, based on article 3.1, activities in which workers are exposed or likely to be exposed to carcinogens or mutagens as a result of their work.

From the above, while the CAD is triggered by the presence of hazardous chemicals at the work place, the CMD is triggered by a narrower scope of application, that is when workers are exposed or likely to be exposed to carcinogens and mutagens. Indeed, there may be situations, such as when chemicals are used only in closed systems, where the workers are not exposed or likely to be exposed, but chemicals are nevertheless present at the work place.

When the relevant chemical substances are within the scope of either Directive, employers are required to perform a risk assessment, prior to taking further action (Art. 4 CAD, Art. 3 CMD).

OELs for chemical substances and 'de minimis' obligations

Both Directives require the establishment of limit values for occupational exposure of workers to certain chemical substances by inhalation and in relation to a specified reference period. However, there are two differences between the CAD and the CMD with regard to OELVs.

Firstly, the CAD foresees the adoption of IOELVs, BOELVs and BLVs (Art. 3), whereas the CMD only envisages BOELVs, set out in Annex III to the Directive.

Secondly, under the CAD, where the health-based OEL is respected within the place of work, it is assumed that the risk has been eliminated and employers will not have to adopt additional risk management measures. However, if the OEL has been exceeded, the employer must take immediate steps to remedy the situations, by adopting preventive and protective measures, which take into account the nature of the limit (Article 6.3,§2). The CMD imposes stricter obligations. It states not only that "exposure shall not exceed the limit value of a carcinogen as set out in Annex III" (Article 5.4) but also requires employers to continue to reduce exposure[168] to as low as level as technically possible, even where the OEL is respected. Therefore, the CMD imposes a *'de minimis'* obligation with regard to exposure, which does not exist under the CAD.

Level of risk considered

The results of the risk assessment will determine whether, and if so which, measures ought to be implemented by the employer. To that effect, a significant difference is noted between the CAD, where a distinction is made between two levels of risk, and the CMD where this distinction does not exist.

The CAD distinguishes between (i) situations where the risk assessment reveals a 'slight risk' to the safety and health of workers and (ii) situations where the risk assessment reveals a 'risk', and implicitly iii) where the risk assessment concludes there is no risk.

In accordance with article 5.4, where only a 'slight risk' has been revealed, the application of general preventive measures set out in articles 6(1), 6(2) of the Framework Directive 89/391 and those set out in article 5.2 of the CAD could be enough. If such general preventive measures are sufficient to reduce the slight risk, then there is no requirement to take further measures . We note that the CAD qualifies the slight risk "because of the quantities of a hazardous chemical agent present in the workplace". As discussed below, there is a need for interpretation to determine whether other considerations can also be taken into account to quantify the risk.

Where the risk assessment reveals a 'risk', which by deduction is higher than a 'slight risk', further measures must be applied to eliminate or reduce such a risk. Article 5.3 specifies that these additional measures are those set out in articles 6, 7 and 10 of the CAD.

To the contrary, the CMD provides no distinction between different levels of risk that could be revealed in the risk assessment. Arguably, since the scope of the CMD requires that workers are exposed, or likely to be exposed, and since carcinogens and mutagens are by definition 'hazardous' substances', there is always some level of residual risk when there is exposure to carcinogens or mutagens at the work place. Consequently, it could be held that the risk assessment to be conducted does not seek to determine 'whether' there is a risk but the degree of risk that is present or expected.

[168] In the case of C/M substances which the CMD treats as non-threshold substances, exposure signifies risk.

Nonetheless, certain employer obligations are explicitly subject to the risk assessment having revealed a risk, such as those listed in article 6.

The absence of a distinction between levels of risk, renders the CMD more stringent than the CAD, which offers a lighter set of obligations incumbent on the employer where the risk assessment only reveals a 'slight risk'.

When is substitution to be considered?

Substitution (also called 'replacement') is a key RMM under the CAD and the CMD but there are important differences between the two Directives. As a general remark, the CAD is more specific regarding the situations in which substitution should be considered, whereas the drafting of the CMD provisions leaves room for potential interpretations. This is discussed further in this section.

There are two cases in which the CAD requires substitution to be considered:

1. Where there is a risk higher than a slight risk (Article 5.3 CAD), article 6.2 of the CAD requires substitution as the preferential measure for eliminating or reducing the risk 'to a minimum';

2. Where there is a slight risk (Article 5.4 CAD) and the general preventive measures taken in accordance with articles 5.1 and 5.2 are not sufficient to reduce the slight risk, without having to reduce it 'to a minimum'. Indeed, specific protective and prevention measures, including substitution, also apply in cases of slight risk, if the general preventive measures are not sufficient to reduce the slight risk. In that case, the risk must be eliminated or reduced to a minimum through further measures.

Under the CMD, there are two main provisions where 'replacement', i.e. substitution, is mentioned. The first is article 4.1, which refers to substitution as a particular method that employers should apply to reduce the use of a carcinogen or mutagen at the work place. The second provision referring to substitution is article 5.1-2, which starts by stating that where a risk is revealed by the risk assessment, workers' exposure must be prevented. The next paragraph states that where substitution is not technically possible, a closed system should be used. We also note that the scope of the CMD under article 3.1 requires that there is or is likely to be exposure to a carcinogen or mutagen. This is in line with the fact that, at the time of adoption of the CMD, the prevailing scientific opinion was that C/M substances have no threshold and, as a result, no level of exposure, however small, can be safe. This means that whenever an activity falls within the scope of the Directive, there is a residual risk, unless the substance is replaced with another substance that is not C/M or a completely closed system is used.

As a worst case scenario in relation to the costs for companies, the analysis in this study is based on the interpretation that the CMD requires substitution to be considered in any case where workers are or are likely to be exposure to a carcinogen or mutagen.

Nonetheless, the circumstances triggering substitution as a RMM are different under the CMD than under the CAD, since the lighter set of obligations that the CAD offers where there is only a slight risk does not explicitly include the obligation to consider substitution as a RMM. This means that substitution will not necessarily be considered as a RMM each time a hazardous chemical agent is 'present' or 'used' at the workplace under the CAD. Such consideration is dependent on the level of risk that is revealed in the risk assessment. To the contrary, under the CMD, once an activity falls within its scope, substitution is considered as a RMM at least in all cases where there is exposure, or likeliness thereof, and thus whatever the level of risk revealed in the risk assessment.

In practice, most Member States have used a similar wording to the CMD when implementing the provisions on substitution. However, certain Member States have adapted the language of the CMD, such as Belgium for example, that explicitly requires the results of the risk assessment to reveal a risk for substitution to be considered.

What are the criteria for deciding on substitutability Once substitution is to be considered as a RMM under either Directive, it must be verified whether substitution must be applied. Both the CAD and CMD include wording reflecting circumstances that may relieve employers from the obligation to substitute. Noticeably, different terms are used to that effect in both Directives.

The CAD requires substitution in article 6.2 "where the nature of the activity permits the risk to be eliminated by substitution". It is up to the employer to evaluate whether the nature of his activity allows for substitution and in doing so, the employer must have regard to the risk assessment carried out.

Under the CMD, article 4.1 requires substitution "in so far as is technically possible". This condition is repeated throughout the hierarchy of RMM and must also be evaluated by the employer. The CMD further specifies that the authorities can request the employer to submit the findings of his investigation. This is not provided in the CAD although one could anticipate that national authorities may foresee the right to request such information under their national laws, as set out in the Czech Republic and Denmark.

It appears that certain Member States have refined the implementation of the substitution requirement by adding criteria. For example: In Austria, substitution is required if the same result can be achieved (by the alternative). In Finland, substitution is required when technically feasible and 'reasonably practicable'. In Denmark, Germany and the UK, economic considerations may be taken into account.[169] Germany also requires detailed documentation including reasons for decisions against substitution to be provided to enforcement bodies on request.

If substitution is not required, what other RMMs apply?

The measures that ought to be taken when substitution is not required vary between the Directives and this may notably be linked to the different objectives the Directives pursue. Indeed, whereas the CAD aims to minimise risks, the CMD aims to minimise exposure. To achieve such goals, the Directives do not require to same RMMs to be implemented when substitution is not possible.

Article 6.2 of the CAD sets out the protection and prevention measures to take in such case and specifies that their application should be consistent with the risk assessment. In that respect, the following measures must be taken in hierarchal order to ensure that the risk is reduced to a minimum:

- Design appropriate work processes and engineering control and use of adequate equipment and materials to avoid or minimise the release of hazardous chemical agents which may present a risk;
- Application of collective protection measures at the source of the risk (ex: adequate ventilation and appropriate organizational measures);
- Where exposure cannot be prevented by other means, application of individual protection measures, including personal protective equipment (PPE).

[169] Consultation for this study

According to the provisions of the CMD, where substitution is not technically possible, articles 5.2 and 5.3 require two other measures to be taken in hierarchal order and in so far as technically possible:

- Ensure that the carcinogen or mutagen is manufactured and used in a closed system;
- Ensure that the level of exposure of workers is reduced to as low a level as 'technically possible'.

While these two sets of RMM measures are different, those set out under the CAD also figure among the list of measures that apply under the CMD "wherever a carcinogen or mutagen is used" (Article 5.5), namely:

- limitation of the quantities of a carcinogen or mutagen at the place of work;
- keeping as low as possible the number of workers exposed or likely to be exposed;
- design of work processes and engineering control measures so as to avoid or minimise the release of carcinogens or mutagens into the place of work;
- evacuation of carcinogens or mutagens at source, local extraction system or general ventilation, all such methods to be appropriate and compatible with the need to protect public health and the environment;
- use of existing appropriate procedures for the measurement of carcinogens or mutagens, in particular for the early detection of abnormal exposures resulting from an unforeseeable event or an accident;
- application of suitable working procedures and methods;
- collective protection measures and/or, where exposure cannot be avoided by other means, individual protection measures;
- hygiene measures, in particular regular cleaning of floors, walls and other surfaces;
- information for workers;
- demarcation of risk areas and use of adequate warning and safety signs including 'no smoking' signs in areas where workers are exposed or likely to be exposed to carcinogens or mutagens;
- drawing up plans to deal with emergencies likely to result in abnormally high exposure;
- means for safe storage, handling and transportation, in particular by using sealed and clearly and visibly labelled containers;
- means for safe collection, storage and disposal of waste by workers, including the use of sealed and clearly and visibly labelled containers.

Accordingly, the CMD requires more RMM to be applied when substitution is not possible than the CAD.

We also note that the requirement of a closed system, which is specifically consolidated in the CMD, is not a measure which is listed under the CAD, except for prohibited substances that are intermediates (Art.9). In practice, this requirement is perceived as very stringent and unique to the CMD. However, it could be argued that such systems could fall under article 6.2(a) of the CAD, within the meaning of 'appropriate work processes' and/or 'engineering controls'. If so, closed systems could be considered as the second RMM within the hierarchal order, in the event that the nature of the activity would not permit substitution to eliminate the risk. This is further supported by the Guidelines on the CAD where closed systems are listed as processes or installations which can be used to reduce risk and are considered a "good solution where chemical agents with a high or average hazard rating are involved".[170]

[170] Guidelines on the CAD, p.30, 33.

Consequently, the CMD requires additional measures to be implemented as RMMs than under the CAD, including the stringent obligation to set up a closed system where substitution is not possible.

X3.2.5 Need for interpretation in the CAD and the CMD

Based on the above analysis, certain provisions and wordings in the CAD and CMD could benefit from greater coherence and/or guidelines refining the interpretation that is to be given. Such actions could ensure a more uniform implementation and enhance industry compliance.

We also note that a majority of Member States have responded in favour to the adoption of additional guidance at the EU or national level to aid the interpretation of the OSH legal framework and/or setting out the 'best available techniques' for preventing or reducing exposure to relevant substances in different industry sectors. More specifically, the reasons behind the Member States' positions included the obtaining of a better harmonisation of protection levels of workers throughout the EU and improving the practical implementation of regulatory provisions.

Therefore, the object of the following section is to addresses certain provisions which may raise such a need for interpretation.

The implementation of substitution

In 2012, the need for further guidance regarding substitution was already identified as a key measure to enhance the use of substitution.[171] It was underlined that the existing guidance at that time, were not practical or easy to implement, particularly for SMEs. We note that the current Practical Guidelines on the protection of the health and safety of workers from the risks related to chemical agents at work (Guidelines on the CAD), date back to 2005.

For smaller enterprises, substitution was perceived as far too complex a process considering the limited knowledge and capacity they can devote to systematic risk reduction. In that respect, the main barriers that were mentioned at the time were the interpretation of hazard data given in SDS, the risk assessment itself and the control of the effectiveness of the assessment. Many EU workplaces concluded that risk assessments should be made easier and more accessible by providing guidance on substitution's fundamentals, i.e. basic components of hazard identification and the inclusion of exposure potential estimation and risk assessment in a same document. Specifications with regard to risk assessments was also suggested by Member States in their consultation responses, as an element that should be included in further guidance.

Under the CAD

Characterization of a risk as 'slight'

Where the CAD provides a distinction between a 'risk' and a 'slight risk', in article 5.4, further guidance on the interpretation of the term 'slight risk' could be useful. The characterization of a risk as 'slight' is a question of proportionality based on a qualitative approach. However, the provision only specifies that a slight risk to workers' safety and health is "due to the quantities' of a hazardous chemical agent present in the workplace". Furthermore, in practice, it has been mentioned that the distinction of risks and subsequent applicable obligations has not been based on the provisions of the CAD and whether the risk is 'slight' or not but rather on common sense, i.e. risks that employers deem to be better dealt with through other measures than substitution. Indication of reference quantities that may be used,

[171] EU Commission, 'Study: Minimising chemical risk to workers' health and safety through substitution', 2012.

such as OELs, or non-exhaustive criteria could help guide employers towards a more consistent characterization of risks as 'slight'.

The Guidelines on the CAD may provide some insight for employers. A brief definition of a risk is provided as "the likelihood that the potential for harm will be attained under the conditions of use and/or exposure". However, these guidelines are primarily intended to assist Member States and are not legally binding. It must also be noted that the general character of the Guidelines on the CAD does not take into account the specificities of Member States' national legislation. Consequently, they may not be the ideal instrument for employers, which may already be confronted with the costs of having to abide with the various implementations of both Directives, in which case the potential additional expense linked to assessing the Guidelines on the CAD may not be conceivable. The most useful Guidelines are likely to be those intended for employers, easy to use and redacted by the national authorities. In that respect, the UK for example, adopted practice guidelines which are integrated into its legislation but few countries have done the same.

Article 5.4 of the CAD includes another element pertaining to the characterization of a risk as 'slight', which may benefit from interpretation, whereby it mentions that in case of a 'slight risk', further RMM do not apply where the general preventive measures of articles 6(1), 6(2) of the Framework Directive 89/391 and article 5.2 of the CAD are "sufficient to reduce that risk". Here again, there is no indication as to when a risk is to be deemed 'sufficiently' reduced to avoid the triggering of additional measures, including the need to consider substitution. Further information on the degree to which the slight risk must be reduced in order to qualify as 'sufficient' could be useful. In the event that 'any' reduction, i.e. the slightest reduction of the slight risk, would be sufficient, this could be specified.

Substitution as a preventive measure?

As set out above, based on article 5.3, 5.4 and 6 of the CAD, substitution as a RMM should be considered either when there is a risk higher than 'slight', or when the risk is 'slight' but the general preventive measures were not sufficient to reduce such risk. However, the Guidelines on the CAD further consider that substation should be considered as a preventive measure and specify that substitution is at least 'desirable', even when the risk is slight, based on two arguments.

First, since article 5.1 of the CAD, makes a reference to article 6(2) of the Framework Directive 89/391, where 6(2)(a) states 'avoiding risks' as one of the general principles of prevention, the Guidelines on the CAD deduce that "risk elimination (i.e. substitution) is actually the first principle for prevention".[172] However, we understand that substitution could also likely fall under 6(2)(f), which sets out "replacing the dangerous by the non-dangerous or the less dangerous" and that neither article 6(1) nor 6(2) set out a hierarchal order within the general principles.

Second, where article 5.2 of the CAD states that: "risks (...) involving hazardous chemical agents shall be 'eliminated', the Guidelines on the CAD establish that: 'the risk due to work involving a hazardous chemical agent is eliminated when the agent disappears. It is therefore desirable to substitute this with another chemical agent or process (...)".[173]

We note that the potential reference to substitution under article 6(2) of the Framework Directive 89/391 is very general and the reference under article 5.2 is not explicit. Additionally, under this interpretation, substitution would be more imperative where there is a slighter risk than when there is a higher risk. This interpretation would also render the CAD almost as stringent as the CMD, whereby substitution would have to be considered in all cases where a risk would be revealed by the risk

[172] Guidelines on the CAD, p.19.
[173] Guidelines on the CAD, p.22.

assessment. In practice, this is not the understanding that seems to be retained by employers, who perceive substitution as a requirement which is more stringent under the CMD.

This demonstrates that there might be a need for interpretation with regard to the circumstances under which substitution should be understood as having to be considered as a preventive measure, under the CAD.

Under the CMD

Consideration of substitution

The main need for interpretation within the CMD pertains to the situations triggering the obligation for employer to consider substitution. This issue was referred to earlier in this section and is articulated around the interpretation to be given to the scope of the CMD laid out in article 3.1, and the provisions in which substitution is brought up, i.e. article 4.1 and 5.2. In that respect, the main question is whether the prior identification of a risk in the risk assessment is required in order to apply substitution, or if substitution must be considered in all cases where a carcinogen or mutagen is used, and/or only subject to workers being exposed or likely to be exposed to such carcinogens or mutagens. The various possible interpretations stem from the following articles:

First, Article 4.1, which states the following:

> *"'The employer shall reduce the use of a carcinogen or mutagen at the place of work, in particular by replacing it, in so far as is technically possible, by a substance, preparation or process which, under its conditions of use, is not dangerous or is less dangerous to workers' health or safety, as the case may be"'.*

The absence of any reference to the disclosure of a risk in the risk assessment, may lead Member States to consider that substitution must be considered by employers in any case where a carcinogen or mutagen is used.

Second, Article 5 is drafted in two paragraphs stating that:

> *1. "'Where the results of the risk assessment (...) reveal a risk to workers' health or safety, workers' exposure must be prevented"'.*
>
> *2. "'Where it is not technically possible to replace the carcinogen or mutagen (...), the employer shall ensure that the carcinogen or mutagen is, in so far as technically possible, manufactured and used in a closed system"'.*

The latter paragraph, setting out the second RMM to apply where substitution is not possible, i.e. a closed system, does not explicitly mention the prior identification of a risk following the risk assessment, unlike the first paragraph of the same article, which clearly states that such prior revelation of a risk is a pre-requisite to preventing exposure. However, the measures to take in order to 'prevent' exposure are not identified. Because the second paragraph sets out the requirement of a closed system, where substitution is not technically possible, there is room for interpretation as to whether this means that substitution and the following RMM are to be considered as measures to 'prevent' exposure and therefore, whether such measures are subject to the prior identification of a risk. If so, then substitution is could be interpreted as having to be considered where the risk assessment reveals a risk to workers' health or safety.

Nonetheless, in both cases, the scope of the CMD, laid out in article 3.1, should be considered as well. Accordingly, the Directive is only applicable to employer activities in which workers are exposed or likely to be exposed to carcinogens or mutagens, as a result of the work they carry out. Therefore, it could be considered that because carcinogens or mutagens are intrinsically hazardous, the requirement that there must be exposure to such substances, or a likeliness of exposure, could mean that a residual risk always exists once activities fall under the scope of the CMD.

However, the scope of application of the CMD could be confronted with today's scientific knowledge, which has expanded to encompass the concept of thresholds for carcinogens and mutagens. In such a case, where an activity would fall within the scope of the CMD, there could be a reference value based upon which a risk assessment may lead to the conclusion that there are no risks to the workers' health or safety. Consequently, based on the interpretation that is to be given to the requirement, substitution will either have to be considered or not. In light of such developments, there might still be a need for interpretation.

In practice, most Member States have used a similar wording than the CMD when requiring substitution. However, as an example, Belgium has adopted a different wording in that its implementing provisions explicitly require the results of the risk assessment to reveal a risk for workers' health or security to trigger the obligation to avoid workers' exposure by substitution.

When is substitution required as a RMM under the CAD and the CMD?

A common element that may need interpretation under both Directives to ensure coherence between the two, relates to identifying the situations in which substitution is required or whether the next RMM should be implemented based on the hierarchy provided in Articles 6.2 of the CAD and 5.2-3 of the CMD.

As previously explained, under the CAD, substitution shall be preferably undertaken except where "the nature of the activity does not permit risk to be eliminated by substitution, having regard to the activity and the risk assessment", whereas under the CMD, substitution is limited "in so far as technically possible". In view of greater consistency in the application of substitution as a RMM, it could be favourable to further elaborate over the meaning of these conditions, within the relevant provision, notably by listing elements that could be taken into account to consider that the nature of an activity does not permit the risk to be eliminated by substitution or that it is not technically possible.

It is difficult to determine how in practice an assessment that the nature of an activity permits the risk to be eliminated by substitution differs from an assessment of when substitution is technically feasible. This difference calls for interpretation, in particular since the Guidelines on the CAD do not appear to make a distinction between the two terminologies. Indeed, the Guidelines on the CAD refer to 'technical possibility' instead of the nature of the activity[174] and set the area of application of substitution under the CAD as follows: (i) where a technically viable substitute exists, and (ii) where its hazard rating is lower than that of the hazardous chemical agent used.[175] Consequently, it appears that the Guidelines to the CAD base the assessment of substitution on its technical feasibility and confirm that employers should take into account this criteria while identifying alternatives. We however have not been able to identify the legal basis within the CAD upon which these conditions apply, and in particular how they relate to article 6.2 of the CAD. The reference to the Framework Directive 89/391 in article 5.1 of the CAD could be invoked but the reference to substitution under such Directive is very general and does not refer to 'technical feasibility'. An analysis of the technical possibility of substitution seems to require to take into account the nature of the activity, but in both

[174] Guidelines on the CAD, p.22, 26-27.
[175] Guidelines on the CAD, p.27.

cases, the availability of substitutes and their capacity to offer a technical alternative would seem to be required. Neither text specifically refers to the 'economic' feasibility of the substitute, but one could argue that it is inherent to an analysis of whether the nature of an activity permits substitution, as the activity may no longer exist if the substitute is not economically viable.

We could not find a clear rationale for the above different language and believe that the terms used in both Directives could lead to various interpretations. Where the intention of the legislator is for the conditions under the CAD and the CMD to be assimilated, as could be deduced from the Guidelines on the CAD, a potential revision of the current wording to that effect would provide greater coherence between the CAD and the CMD.

The relative broadness of the conditions has led Member States to supplement it with other criteria, such as the economic viability of the possible alternative (e.g. Denmark, Germany and the UK).

In comparison, under REACH, the 'substitution principle' requires a comparison of the risk profiles of different substances and may prevent authorisation of a substance of very high concern, including a CMR, when there are suitable alternative substances or technologies that are economically and technically viable (see REACH Article 55 and Recital 69). Indeed, when listed in Annex XIV of REACH, CMR 1A/1B can be authorised pursuant to Article 60.2 of REACH if the risks arising from their CMR properties are adequately controlled or failing this, under Article 60.4 if their socio-economic benefits outweigh their risks and if there are no suitable alternatives or technologies. Article 60.5 then specifies the conditions under which alternative substances and technologies shall be assessed. The 'adequate control route' is not available for substances, including CMR 1A/1B "for which it is not possible to determine a threshold in accordance with Section 6.4 of Annex I" of REACH. These articles do not discriminate between CM and R substances.

Conclusions

A review and comparison of the key provisions of the CAD and the CMD, such as the provisions setting up the scope of application of these Directives, the circumstances triggering the need to consider substitutes and to apply substitution, reveals a need for greater coherence between the provisions of both Directives and potential interpretations of such provisions. The aim would be to ensure a more consistent implementation within EU Member States in view of a more systematic and easy application by employers.

Since both Directives require implementation by the Member States, they may adopt different interpretations of certain provisions where such possibility exists and this may be reflected in their legal text and/or, even when using the same legal text, in their national practices.

Additionally, the CAD and the CMD being Directives of minimum harmonization, Member States may prescribe additional requirements that go beyond those set out in the CAD and/or CMD. However, considering possible room for interpretation discussed above, an analysis of whether a given national measure goes beyond or rather below the minimum harmonization is particularly difficult. For example, whether the Directives allow Member States to allow employers to take into account economic considerations in the analysis of substitutes could be debated.

X3.3 Existing national legislation[176]

X3.3.1 Introduction

The following sources were used:

- Milieu/RPA report[177] from 2012;[178]
- COWI/Milieu/IOM, Country Summary Reports of 2015;[179]
- Desk research for this study: country by Country Reviews for CMR update 1 January 2014 (hereafter the 2018 Report);
- Responses provided by EU Member State National Authorities to the questionnaire on reprotoxins, (hereafter the 2018 questionnaire);
- Follow-up communication with Member States.

X3.3.2 Typology of national measures in the EU

As directives of minimum harmonization, the CAD and the CMD allow Member States to adopt more stringent measures than those set out therein. Consequently, the Directives have not been implemented in the same way throughout all the Member States. While each national system has its own specificities, EU Member States have broadly selected to transpose the CAD and CMD in the following three ways:

- National measures that transpose the two Directives in two separate legal instruments
- National measures that transpose the two Directives in one legal instrument

[176] The following report is based on information that has been provided through country reports on their implementation of the CAD and CMD in the following documents:
- Country by Country Reviews for CMR update 1 January 2014, compiled by Verisk 3E and reflecting the countries' situations as of April 2018 (hereafter the '2018 Report');
- The RPA, Milieu, *Reports on the implementation of legislation to protect workers from chemical exposure in the 27 Member States and the EEA countries, Supporting Documents to the Final Report for the analysis at EU-level of health, socio-economic and environmental impacts in connection with possible amendment to CMD of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens and mutagens at work to extend the scope to include category 1A and 1B reprotoxic substances*, October 2012 (hereafter the '2012 Report' or 'RPA, Milieu Report, 2012');
- Responses provided by EU Member State National Authorities to the questionnaire on reprotoxins, sent by RPA and reflecting the countries' situations as of August (hereafter the '2018 questionnaire');
- follow-up questionnaires.

This report does not take into account additional national measures that may have been adopted to complement the main transposition measures of the CAD or CMD, by separately dealing with specific points of the Directives such as the establishment of OELs/BLVs or specific substances (most commonly lead or asbestos).

[177] DG EMPL report on "Analysis at EU-level of health, socioeconomic and environmental impacts in connection with possible amendment to Directive 2004/37/EC to extend the scope to include category 1A and 1B reprotoxic substances". Study contract VC/2010/0400

[178] The information in Milieu/RPA (2013) has been updated to the current time and complemented with any new information that has become available. Additional new research has been included for the Member States not included at that time (Croatia), non-EU EEA Countries (Norway, Iceland and Liechtenstein) and major EU trading partners (Australia, Brazil, Canada, China, Indica, South Korea, Switzerland, USA).

[179] COWI, Milieu and IOM , "Evaluation of the EU Occupational Safety and Health Directives", individual country summaries, VC/2013/0049, June 2015.

- Implementation in a series of national measures

National measures that transpose the two Directives in two separate legal instruments

In the majority of the EU Member States, the CAD and CMD were transposed through two separate legal instruments. This is the case for the following 10 countries: Croatia, Denmark,[180] Greece, Latvia, Luxembourg, Poland, Romania, Slovakia, Slovenia and Spain.

In doing so, these Member States have largely replicated the texts of the two Directives, including their respective scope of application, and have thus not extended the CMD to cover reproductive toxicants. However, this does not mean that the transpositions are identical. In some cases, national legislation provides further details or relies on wording that is different from the initial provisions set out in the CAD and CMD. In other cases, some provisions have been left out of the transposing legislation. For example, several Member States have not transposed the requirements of Article 9 of the CMD pertaining to access to risk areas, such as Latvia and Poland among others.

By way of example, Spain has included the provisions of the CMD in the Royal Decree 665/1997 on the protection of workers from risks related to exposure to carcinogens at work, whereas the provisions of the CAD are transposed by Royal Decree 374/2001 on the protection of health and safety of workers from risks related to chemical agents at work. These decrees almost identically transpose the provisions of the two Directives with some additional details provided on occasion, notably with regard to the information that should be provided to workers under the CMD, and the way in which the risk assessment should be conducted under the CAD.

Transposition of the two Directives in one legal instrument

Other EU Member States have opted to implement both Directives into their existing national legislation, such as the Labour Code, Well-being At Work Code or other legislation that covers a wider range of subjects. Member States that have used this method have generally opted to extend the overall scope of the CMD to cover Reprotoxins or extended the provisions of certain CMD provisions to cover a broader range of chemicals than CMs only, therefore including reprotoxins indirectly. However, certain Member States have not extended the scope of the CMD, such as in Italy.

Transposition through a single instrument has been achieved in the following two ways:

A single legal instrument with separate sections implementing the CAD and the CMD

This is the case in France, which transposed the two Directives into the French Labour Code, Belgium where the Directives are transposed through the Well-being At Work Code (BCW) and Italy where such provisions are included in the Legislative Decree No.81/2008. The scope of these instruments tends to cover more than the transposition of the CAD and CMD, and other EU legislation may also be transposed therein.

It is of note that in 2017 Belgium changed its implementation and went from having two separate Royal Decrees respectively implementing the CAD and the CMD, to integrating the provisions of both

[180] Denmark responded that they are currently merging their executive order on Chemical agents (covering reprotoxic substances) and their executive order on Carcinogens. However, the merging will affect the form and the wording of the executive order but will not affect the content or the protective level and is as such unrelated to reprotoxic issues.

Directives into the BCW.[181] The BCW regroups existing legislation into a single, coordinated instrument with ten separate parts. Part VI of the BCW concerns chemical agents and CMRs. It is sub-divided into separate titles, the first of which is applicable to all chemical agents and transposes the provisions of the CAD. The second title is dedicated to CMRs and transposes the provisions of the CMD.

A single legal instrument with a unique system for all chemicals within the scope of the CAD and CMD

In the UK and Germany, a single national legal instrument is used to implement both the CAD and the CMD. However, the legislation sets up a unique system which appears to combine the requirements of the CAD and the CMD. These systems are difficult to analyse from a CAD and CMD transposition perspective because certain measures from the CMD, limited to carcinogens and mutagens under EU legislation, are extended to other chemical agents, while other specific measures may still apply to CM (UK) or CMR (DE) substances only.

Germany has combined the requirements of the CAD and the CMD into the 2010 Hazardous Substance Ordinance, which is generally applicable to 'hazardous substances' for which it provides an extensive definition. However, the Ordinance is divided into sections which do not have the same scope. All substances which fall under the scope of the Ordinance are subject to a multi-tiered risk management system under which employers must first carry out a risk assessment. Employers must preferably substitute hazardous substances and where the risk assessment identifies occupational exposure to such substances, employers must comply with basic obligations and apply general protection measures.[182] If these measures are not sufficient to rule out the risk of oral, dermal or inhalation exposure, supplementary protective measures must be taken.[183] The 2010 Hazardous Substance Ordinance has extended certain CMD provisions too all substances for which the risk assessment has revealed a risk, therefore including reprotoxins. This is notably the case regarding substitution, which is a general requirement. However, there are also certain CMD provisions which have either deliberately been extended to reprotoxins (e.g. demarcation or the assessment of exposure by measurements), or deliberately not been extended to reprotoxins (e.g. record keeping for 40 years or health surveillance).[184] The 2010 Hazardous Substance Ordinance also provides for exemptions,[185] and is supplemented by technical rules on hazardous substances which may be followed on a voluntary basis, the compliance of which creates the assumption that the employer conforms with the Ordinance.

The United Kingdom (UK) has set out its requirements in the 2002 Control of Substances Hazardous to Health Regulations (COSHH), which although it globally implements the requirements of the CAD and CMD, has a broader scope and particular system. It covers all substances which qualify as being 'hazardous to health' according to the definition provided therein. COSHH requires the performance of a risk assessment where the work carried out could expose employees to any substance hazardous to health, which includes the consideration of elements both from the CAD and the CMD. There is a general obligation to prevent employee exposure to such substances, but where this is not reasonably possible, COSHH imposes a duty of control through the adoption of appropriate protection measures.[186] Where the exposure involves CMs or biological agents, additional measures are required.

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[181] The CAD was transposed through Royal Decree of 11 March 2002 on the protection of workers' health and safety against risks related to chemical agents at work. The CMD was transposed in the Royal Decree of 2 December 1993 regarding the protection of workers against risks related to exposure to carcinogens and mutagens at work.

[182] Milieu/RPA Report, 2012, p.132 ; Art. 6-8 of the 2010 Hazardous Substance Ordinance.

[183] Milieu/RPA Report, 2012, p.132 ; Art. 9 of the 2010 Hazardous Substance Ordinance.

[184] Milieu/RPA Report, 2012, p.132 ; Art. 10 of the 2010 Hazardous Substance Ordinance.

[185] *Ibid.*

[186] Regulations 5-13 COSHH.

The legislation also allows for exemptions regarding certain requirements but this possibility is not specific to reprotoxins and has rarely been used.

Implementation in a series of national measures

In several EU Member States, the CAD and the CMD have been transposed into a number of national measures which may be a part of legal instruments covering the implementation of other Directives as well. In that respect, certain EU Member States have an overarching act on occupational health and safety that gives the authority to implement provisions set out in more specific legislation, creating a pyramidal structure, where several acts may contain obligations for employers. In such a case, the provisions of the two Directives are scattered across several measures, generating a complicated situation to analyze from an implementation stand-point. Among the countries following this typology, there does not appear to be a particular trend to include reproductive toxicants with carcinogens or mutagens.

Countries that follow this typology include, e.g. Austria, Bulgaria, Cyprus, Czech Republic, Estonia, Finland, Hungary, Ireland, Lithuania, Malta, the Netherlands and Portugal. By way of example:

Malta may serve as an illustration of a pyramidal structure that comprises a number of tiers. The main statute based upon which other legal acts were adopted is the Occupational Health and Safety Authority Act. This measure allows the responsible Minister to adopt subsidiary legislation (S.L.) to regulate, monitor and enforce health and safety requirements at the workplace and the prevention of risks related thereto.[187] Accordingly, Malta has adopted two pieces of subsidiary legislation to implement the legal requirements of the CAD and CMD, respectively S.L. 424.24 (LN 227/2003) on the Protection of the Health and Safety of Workers from risks related to Chemical Agents at Work Regulations, and S.L. 424.22 (LN 122/2003) on the Protection of the Health and Safety of Workers from risks related to Carcinogens and Mutagens at Work Regulations. Within Section 7 of S.L. 424.24 on the arrangements to deal with accidents, incidents and emergencies, reference is made to additional specific regulations for the first-aid, fire-fighting, evacuation, warning and communication measures that must be taken. These are set out in S.L. 424.13 on Work Place (First Aid) Regulations, S.L. 424.15 on Work Place (Minimum Health and Safety Requirements) Regulations and S.L. 424.16 on Work Place (Provision of Health and, or Safety Signs) Regulations.[188]

The Netherlands has transposed the two Directives through three acts which together form the Working Conditions Legal Instruments: Working Conditions Law of 18 March 1999, Working Conditions Decree of 15 January 1997 regarding the safety, health and wellness in the workplace and the Working Conditions Regulation of 12 March 1997 implementing provisions of the Working Conditions Decree. All three acts implement the CAD, while the CMD is implemented through the Decree and Law. Provisions implementing the legal requirements of both Directives may therefore be found in the same measures.

The Czech Republic has also transposed the Directives in several pieces of legislation, which range from general requirements, found in superior legislation, to specificities, which are provided in lower legislation. First, the general requirements on occupational health protection law are given in the Labor Code (Law 262/2006) and the Public Health Law (Law 258/2000). Next, the legal act which transposes the CAD and the CMD is Law 309/2006. However, the detailed requirements of both Directives are found in Government Decree 361/2007, determining the conditions for the protection

[187] Milieu/RPA Report, 2012, p.248.

[188] Where these reference measures do not implement the CAD legal requirements, Malta could potentially fall under the approach set out in section 2.2 a).

of health at work. Moreover, these measures are completed by the Government Decree 432/2003, laying down conditions for job categories, limit values of biological exposure tests, sampling conditions of biological material for biological exposure tests and requirements for reporting work with asbestos and biological agents.[189] Additionally, the Czech Republic has a law on chemical substances and preparations which sets out the procedures for determining which substances are reprotoxic, i.e. Law 365/2003.[190]

X3.3.3 Third country measures and approaches

Non-EU EEA countries and Switzerland

Among third countries, it is the non-EU EEA (and EFTA) countries which have the closest system to the EU's. Since the CAD and CMD were incorporated into the EEA Agreement, these three countries have transposed the two Directives into their national legislation, while including their national specificities. The same applies to Switzerland. The EEA countries and Switzerland do not follow a common typology. Where Iceland has transposed the two Directives through two separate regulations, respectively transposing the CAD and the CMD, Norway has transposed the two Directives into two measures with broader scopes and Switzerland has incorporated the Directives in a broad single instrument, which forms its primary legislation regarding the country's chemical regime. Liechtenstein has used a more particular method by cross-referring the CAD and the CMD in national legislation and declaring them directly applicable, as *lex specialis*, in Liechtenstein.

Iceland and Norway have also extended at least part of the scope of their national measures dealing with carcinogens and mutagens to include reprotoxic substances, although Norway also has specific provisions for carcinogens and mutagens only.

Non-EEA/EFTA third countries

Legal frameworks

With the exceptions of India and the State of California, none of the other non-EEA countries appear to have adopted specific legal acts for occupational exposure to CMR substances. These substances fall under broader measures which may deal with chemicals or workplace safety and health in general.

Country	CMRs treated same as other chemicals	R treated differently
Australia	Yes	No
Brazil	Yes	No
Canada	Yes	No
China	Yes	Questionable
India	Yes, with exception	Selected employment of women only
Japan	Yes	No
USA	Yes, except California (see below)	California only

By way of example, Brazil has a series of standards to deal with occupational health, environmental risk prevention programs, occupational health examination programs and safety signs. No measures appear to be specific to chemical agents or CMRs at the workplace.

[189] Amended by Decree 107/2013.
[190] Milieu/RPA Report, 2012, p.61.

To the contrary, in India, while there is no specific regulatory information for CMRs, there is a regulation to protect female workers from occupational exposures to "reprotoxic substances" in the context of workplace safety. This approach applies specifically to the "female workers." Under *The Factories Act, 1947*, employment of women in hazardous processes which might cause a potential effect on their reproductive health is restricted.

Substantive requirements

Generally speaking, there appears to be a greater focus on carcinogens than on mutagens or reprotoxins in a number of the third countries, including Brazil, South Korea and the USA. Another common feature is that none of the non-EEA/EFTA third countries seem to have a system in place that requires the substitution of C, M and/or R as the main risk management measure to be taken when dealing with such chemical agents. Their main provisions to regulate such substances appear to be through the establishment of OELs and the communication of hazard information through labelling and classification requirements, mostly following those of the GHS.

Contextualising third country measures

The sectors in which the local industry is active can explain why certainly measures have been implemented or not in some of the third countries. For example:

Norway has adapted its legislation to accommodate the specificities of its dominant fishing and petroleum industries. It has regulations pertaining to petroleum activities, in which a particular paragraph deals with the chemical health hazards related to such activities, and Regulations concerning the working environment, health and safety of workers on board ships.

Additionally, countries may also decide to adopt more specific measures following major events and media coverage. This was also the case for Norway where CMRs became a relevant topic in 2007-2008 after a series of accidents led to workers' exposure to carcinogenic and reprotoxic substances and a lot of media attention was brought upon the cases.

Example of an 'advanced' approach: California's Prop. 65

Within the last year, the USA has seen a remarkable surge in interest in developmental effects from chemicals, as the US state California has fully implemented its newest regulation under the *Safe Drinking Water and Toxic Enforcement Act of 1986*, better known as Prop 65. Although officially and legally the extent of the legislation is confined to the State of California, it has affected all interstate commerce within the USA due to its stringent labelling requirement on anything sold or available through internet commerce to residents of the State of California. The details of the rather stringent labelling requirements themselves are beyond the scope of this document especially since these are primarily aimed at consumers rather than occupational uses, although those are included as well. The labelling is required to state that "This product can expose you to chemicals including Chemical X which is/are known to the State of California to cause cancer/ birth defects or other reproductive harm" (with various modifications). The labelling regulation which went into full effect on 30 October 2018, gained massive attention especially given the breadth of chemicals it includes (Prop 65 is based on a list of well over 300 substances considered to be reprotoxins). Additional confusion is caused by the so-called Safe Harbor provisions which provides *de minimis* exposure levels for some chemicals, below which such warnings are not required.

There are four aspects which are totally different from regulations elsewhere:

7. The presence of *de minimis* or Safe Harbor total exposure limits for selected chemicals, above which a warning is required;
8. The absence of the word mutagenic in the regulation although the presence of M1 classification may be inferred from the "birth defects" language;
9. The applicability of the regulation to both direct and indirect, environmental human exposures;
10. The inclusion of drugs in a consumer-aimed regulation.

Safe Harbor limits are (generally) based on total exposure not exposure limit concentrations contrary to most exposure limits presently in place (one might argue that Biological Limit Values are measures of total exposure). The concept of *de minimis* limits in the regulation of carcinogenic or developmental effects is also quite rare.

Contrary to most of the world, including the EU where carcinogenic and mutagenic (and rarely reproductive effects) are regulated as similar/one entity(s), here carcinogenic, birth defects and developmental effects are all included. One can argue that inclusion of birth defects might be considered equivalent to an M1(A) GHS/REACH classification.

A regulatory approach that mixes environmental human (secondary to releases into the environment) and direct (consumer) human exposures is also quite rare. Here the Safe Harbor levels may also apply to environmental exposures but this has been considered murky.

Drugs, including aspirin, are included in the Prop 65 list. Again, most other regulations consider drugs separately from all other chemicals.

All together Prop 65 by default has driven the adoption and analysis of developmental effect labelling for nearly all US products/articles, without it being a federal, nation-wide law with associated regulations.

X3.3.4 Review of existing proposals

The questionnaires asked EU Member States whether they are contemplating or in the process of changing their national transposition legislation. Almost all Member States have replied that they have no plans to change their national regulation of reprotoxic substances.

Sweden has submitted a proposal to amend the Chemical Hazards in the Working Environment (AFS 2011:19) which should notably introduce clarifications on what is meant by chemical products and chemical hazards, modifications to markings and the introduction of OELs instead of permits for a number of substances. Additionally, the Provisions on Hygienic Exposure Limits (AFS 2015:7) was replaced as of 21 August 2018 by AFS 2018:1, which will amend Swedish OELs for reprotoxic substances.

While France's legislation is not under revision, the French Agency for Food, Environmental and Occupational Health & Safety, responsible for the development of OELs, has proposed atmospheric limit values for six substances since 2017. The Agency has also recommended BLVs and BRVs to improve the monitoring of exposure in workers to several substances.

Ireland has also proposed additions or changes to the OELV in the 2016 Code of Practice for the Chemicals Agents Regulations, which may concern reproductive toxins.

Denmark responded that they are currently merging their executive order on Chemical agents (covering reprotoxic substances) and their executive order on Carcinogens. However, the merging will

affect the form and the wording of the executive order but will not affect the content or the protective level and is as such unrelated to reprotoxic issues.

Germany responded that their new "Mutterschutzgesetz"[191] recently entered into force on 1st January 2018 and it contains several measures concerning pregnant women. It also includes specific safety measures for possible contact with reproductive toxic substances.

It must also be noted that Member States are gradually implementing Directives 2017/164/EU, which notably establishes a fourth list of indicative OELs, and Directive 2017/2398/EU, which amends the CMD. Luxembourg for example deposed a bill for the Regulation transposing Directives 2017/164/EU in March 2017, which was still in legislative procedure as of 27 March 2018. Spain intends to implement Directive 2017/2398/EU by 17 January 2020 and is also in the process of changing certain OELs in 2019.

X3.4 Synthesis of findings

X3.4.1 Regulation of reprotoxic substances

Eight EU Member States have taken advantage of the fact that the CAD and CMD are 'minimum harmonization' directives and have either extended the overall scope of their national legislation transposing the CMD to cover reprotoxins, or extended one or several provisions of the CMD to either reprotoxins or a broader range of chemical agents than just carcinogens and mutagens and therefore covering reprotoxins. This is the case in Austria, Belgium, Czech Republic, Finland, France, Germany, Sweden and the United Kingdom. Where such initiatives have not been taken, reprotoxins remain under the scope of the national legislation that has transposed the CAD.

As a result, there is a large variation as to the legal requirements that apply to reproductive substances across EU Member States.

Three approaches may be distinguished among the EU Member States regarding the legal requirements they impose on reprotoxic substances:

- EU Member States that have not extended the CMD provisions to reprotoxins;
- EU Member States that have explicitly extended CMD provisions to reprotoxins; and
- Other approaches.

Table X3-2: Summary of national legislation in the EU-28

Member State	A: CAD & CMD in one piece of legislation?	B: Same rules for CMs and Rs?	C: Substitution of Rs whenever workers exposed or likely to be exposed?	D: Closed system explicitly required as second RMM for Rs?	E: Exposure minimisation requirement for Rs?	F: CAD 11 R IOELVs binding?	G: Record keeping for >40 years for Rs?
Austria	No	Yes (except G)	Yes	Yes	Yes	Yes	Yes
Belgium	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[191] Mutterschutzgesetz available at: https://www.gesetze-im-internet.de/muschg_2018/MuSchG.pdf

Table X3-2: Summary of national legislation in the EU-28							
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Bulgaria	No	No	No	No	No	Yes	Yes[192]
Croatia	No	No	No	No	No	Yes	No
Cyprus	No	No	No	No	No	Yes	No
Czech Republic	No	Yes	Yes	Yes	Yes	Yes	Yes
Denmark	No	No	No	No	Yes	Yes	No
Estonia	No	No	No	No	No	Yes	No
Finland	No	Some (only C)	Yes	No	No	No	No
France	Yes	Yes	Yes	Yes	Yes	No	Yes[193]
Germany	Yes	Some	Yes	Yes	Yes (exempt if below OEL)	Yes	No
Greece	No	No	No	No	No	Yes	No
Hungary	No	No	No	No	No	Yes	No[194]
Ireland	No	No	No	No	No	Yes	No
Italy	Yes	No	No	No	No	No	No
Latvia	No	No	No	No	No	Yes	No
Lithuania	No	No	No	No	No	No	No
Luxembourg	No	No	No	No	No	Yes	No
Malta	No	No	No	No	No	Yes	No
Netherlands	No	No	No	No	No	Yes	No
Poland	No	No	No	No	No	Yes	No
Portugal	No	No	No	No	No	No	No
Romania	No	No	No	No	No	No	No
Slovakia	No	No	No	No	No	Yes	No
Slovenia	No	No	No	No	No	Yes	No
Spain	No	No	No	No	No	Yes	No
Sweden	No	Yes	Yes	Yes	Yes	Yes	No
United Kingdom	Yes	Some	Where exposure	No	No	Yes	Yes
Total % (Yes)	17.8%	17.8% (or 28,5% if include 'some')	25%	21.4%	25%	78.5%	21.4%
Note: 1: Germany: slight risk rule available for Rs. Sources: Milieu/RPA 2012, COWI reports, Consultation Round 1, Consultation Round 2 (if a Member State says an aspect would have to change, e.g. Italy, we can presume it is not yet in place)							

[192] Health records: 50 years (Ordinance No. 3 of 25 January 2008 on conditions and order for implementation of activities of occupational medicine services)

[193] Medical records: 50 years (R4624-22 to 28)

[194] But 50 years for carcinogens

EU Member States that have not extended the CMD provisions to reprotoxins

The majority of EU Member States have not adopted more stringent obligations for reprotoxic substances than those set out in the CAD. Therefore, in these Member States, reprotoxic substances remain covered under the national legislation transposing the obligations of the CAD and are only subject to the legal requirements set out therein.

The countries that have opted for this approach mainly correspond to those that have also chosen to transpose the CAD and the CMD through two separate legal instruments. This is the case in Poland, Denmark, Romania and Spain. These countries also tend to maintain the delineation between the scopes of the two Directives: the legal instrument transposing the CAD is generally applicable to hazardous substances, whilst the national measure implementing the CMD is restricted to CMs.

For example, Romania has two main acts transposing the CAD and CMD: Governmental Decision No.1218/2006 and No.1093/2006, respectively. These acts transpose the requirements of each Directive with very few alterations. The scope of Governmental Decision No.1093/2006 reproduces the legal requirements of the CMD and its scope of application, which is limited to CMs. Consequently, reprotoxins remain covered under the national provisions transposing the CAD requirements, i.e. Governmental Decisions No.1218/2006 and the corresponding legal requirements.

In addition, some EU Member States that have transposed the CAD and CMD in one or more than two legal instruments have also chosen not to extend the scope of the CMD to reprotoxic substances. This is the case in Italy, which implements the two Directives through a single measure, and Hungary, which relies on a number of legal instruments.

Italy has a single piece of legislation which transposes both the CAD and the CMD, Legislative Decree No.81/2008. The instrument has separate titles for the provisions which transpose the legal requirements of each Directive, and title IX, which covers hazardous substances, is sub-divided into separate sections for chemical agents and CM substances. As the latter section is not extended to cover reprotoxins, such substances remain under the scope of the sub-title dedicated to all chemical agents. The way the different chemical agents are regulated in the legislative decree therefore largely reproduces the scopes of the CAD and CMD.

EU Member States who have explicitly extended some or all CMD provisions to reprotoxins

As mentioned above, some EU Member States have extended the scope of their national legislation transposing the CMD to cover reprotoxic substances, subjecting them to the more stringent rules set out in the CMD. This approach is often characterized by the inclusion of a specific reference to reprotoxic substances in the national legislation transposing the CMD. To define reprotoxins, Member States either refer to the CLP classification or provide specific definitions. Those that have incorporated an explicit reference to reproductive toxins when transposing the provisions of the CMD into their national legislation, notably include Austria, Belgium, Czech Republic and France.

Belgium and France have similar systems whereby a single instrument is used for the transposition of both the CAD and CMD but separate sections are provided to deal with chemical agents and CMRs. In both countries, reprotoxins have been added into the scope of the provisions transposing the legal requirements of the CMD. Accordingly, the relevant sections no longer refer to CMs but to CMRs. Both countries define reprotoxins as a substance or mixture that meets the criteria of classification as Category 1A/1B of reprotoxic substance, as set out in Annex I of the CLP.[195]

[195] Art. VI.2.2, §3 Belgian Code of Well-being ; R.2212-60 French Labor Code.

France also allows the Ministers of Work and Agriculture to provide an additional definition in a joint act. According to the information upon which this report is based, no such act has been adopted.

However, not all EU Member States include reprotoxins by referring to the CLP. As an example, the Czech Republic has implemented the requirements of the CAD and CMD through several instruments which do not all have the same scope. Nevertheless, the main measure implementing the specific requirements of both the CAD and the CMD is Government Decree 361/2007, which applies to reprotoxins of Categories 1 and 2 as defined in the Law on Chemical Substances and Preparations 365/2003. This law states that reprotoxic substance are substances or preparations which when inhaled, digested or absorbed through the skin may cause or exacerbate non-hereditary adverse impacts on the offspring or harm male or female reproductive capability. Article 5 further elaborates over the definition of such substances and states that this is determined by means of a calculation set out in another implementing regulation.[196]

Other approaches

Germany and the UK have singular approaches which have been detailed in section A2.3.1 and seem to combine the legal requirements of the CAD and the CMD. Both countries have implemented the CAD and the CMD through a single measure that has a broad scope and covers 'hazardous substances' in Germany, or 'substances hazardous to health' in the UK.

Moreover, Germany has a set of specific provisions that are applicable to CMRs while the UK has a set of provisions applicable only to CMs. However, these specific requirements are not applicable under the same circumstances as laid out under in the CMD, owing to the specificity of each country's system.

As a brief summary, Germany has combined the requirements of the CAD and the CMD into the 2010 Hazardous Substance Ordinance which is applicable to 'Hazardous Substances'. All covered substances are subject to a specific multi-tiered risk management system that gives rise to obligations where a risk is identified and includes potential exceptions. However, where a CMR substance is involved, additional special protective measures must be implemented. Through this specific system, Germany appears to combine the requirements of the CAD and CMD although certain CMD provisions have either deliberately been extended to cover reprotoxins, or deliberately exclude reprotoxins.

The United Kingdom has set out its requirements in the 2002 Control of Substances Hazardous to Health Regulations (COSHH), covering all substances that qualify as being 'hazardous to health' according to the definition provided therein. COSHH requires the performance of a risk assessment where the work carried out could exposure employees to any substance hazardous to health, which includes the consideration of elements both from the CAD and the CMD. There is a general obligation to prevent employee exposure to such substances, but where this is not reasonably possible, COSHH imposes a duty of control that entails the adoption of appropriate protection measures.[197] Where the exposure involved CMs or biological agents, additional measures are required.

Additionally, Finland has a unique approach since it is the only country which appears to have a separate instrument to deal with reprotoxins. Indeed, Finland adopted the Governmental Decree on Agents Causing Risk to Reproductive Health in Work and the Prevention of Such Risk (603/2015), which lays down provisions on chemical, biological and physical agents causing risk to reproductive health in work. The Decree notably covers reprotoxins of Cat. 2 and calls for the replacement of agents that are hazardous to reproductive health when technically feasible and reasonably practical. The other

[196] Milieu/RPA Report 2012, p.62.
[197] Regulations 5-13 COSHH.

obligations amount to a combination of those of the CAD and the CMD. However, all the requirements set out in the Decree are also applicable to carcinogens and mutagens but specific requirements limited to carcinogens and mutagens exists as well.

X3.5 National requirements going beyond the CAD and CMD

X3.5.1 Risk assessment measures

The majority of EU Member States have implemented a series of additional requirements for the determination and assessment of risks, in comparison to those set out in article 4 of the CAD and article 3 of the CMD. Based on the available information, certain measures appear to be recurring among several EU Member States, while others are unique to a particular EU Member States.

The list hereunder is not exhaustive as such a compilation would require the analysis of each and every measure taken by EU Member States in view of implementing provisions related the CAD and CMD.

Prior to providing a list of such measure, the following table offers a reminder of the differences between the CAD and the CMD with regard to the performance of risk assessment.

Table X3-3: Differences between the CAD and CMD (risk assessment)

	Chemicals at Work Directive (CAD)	Carcinogens and Mutagens Directive (CMD)
Risk assessment	• Determine whether hazardous chemicals are present at the work place (Art.4.1) • If yes, perform a risk assessment (Art.4.1) – List of particulars to be considered in the risk assessment – Obligation to obtain additional info from supplier/other sources • Consider maintenance work	• Determine whether workers are likely to be exposed to C&R as a result of their work (Art.3.1) • If yes, perform a risk assessment → determine the exposure & RMM – Consider all routes of exposure (absorption and/or through skin) Consider workers at particular risk (Art.3.2)

In addition to the provisions in the CAD and CMD, some Member States have adopted further requirements than those in the CAD and CMD, see table below.

Table X3-4: National requirements that go beyond those set out in the CAD (Risk assessment)

	Chemicals at Work Directive (CAD) Article 4	Carcinogens and Mutagens Directive (CMD) Article 3
Recurring	• The risk assessment must be in written form (BE, GD)	• Imposing a fixed period after which a new risk assessment must be performed, such as every one to three years (BE, CZ, DK, IT, HU, LV) • Listing more situations or providing additional details, under which the review of the risk assessment should take place (UK, IT, SE) – E.g.: in the UK, it must be held without delay if:

Table X3-4: National requirements that go beyond those set out in the CAD (Risk assessment)		
	Chemicals at Work Directive (CAD) Article 4	Carcinogens and Mutagens Directive (CMD) Article 3
		○ there is reason to suspect that the risk assessment is no longer valid; ○ there has been a significant change in the work to which the risk assessment relates; or ○ the results of any monitoring carried out in accordance with regulation 10 show it to be necessary, – E.g.: in Italy a new assessment should be made whenever a change is made to the production process (if the alterations are significant for the safety or health on work) – E.g: in Sweden the risk assessment must be updated when new information appears which has a bearing on the risk scenario • The risk assessment must be in written form (CY, DK, GD)
Individual	• The employer must determine whether hazardous chemical agents are present or can be present at the workplace (BE). • Where a justification is provided it must be in written form and submitted to the prior opinion of the Committee on the Prevention and Protection of Work (BE). • Where work activities carry some risk, the employer must promptly take exceptional measurement of work conditions if the company's health prevention department or a public health authority requests it (CZ). • Employers, when assessing the risks derived from exposure by inhalation of a dangerous chemical agent, must measure the concentrations of the agent in the air, in the breathing zone of workers and compare the result with the relevant occupational exposure limit value (ES). • Employers in their assessment must take into account: (ES) – Any other factor that influences the magnitude of the risks related to normal and accidental exposures. – Any other working conditions influencing other risks associated with the presence of agents in the	• Employer must notify the competent authority responsible for inspections together with the Croatian Institute for Health and Safety at Work within 30 days prior to the commencement of production and use of carcinogens and/or mutagens (HG). • The Croatian Institute for Health and Safety at Work has drawn up a form for worker exposure to carcinogenic and/or mutagenic substances, with the necessary information in order to keep records, which employers must complete for each worker who is exposed or could be exposed to CM substances (HG). • Necessary to submit notifications whenever exposure changes occur (substance type, amount of worker exposed, length of exposure) and after exposure to carcinogens / and / or mutagens (HG). • Where there is an assessment of the risks from exposure to reprotoxic substances: Record keeping of information over the average quantity of substances manufacturer or used every year or that is present in storage, and the number of employees generally performing labour in the workplace where the substances are present, and the type of labour usually involving the substance (NL). • In order to carry out the risk assessments, the employer must inter alia identify carcinogenic substances, measure the concentration of carcinogenic substances in the breathing zones at workplaces, and order cytogenetic examinations (HU) • The assessment must not only include the nature, degree and duration of workers

Table X3-4: National requirements that go beyond those set out in the CAD (Risk assessment)		
	Chemicals at Work Directive (CAD) Article 4	**Carcinogens and Mutagens Directive (CMD) Article 3**
	workplace, such as risks related to fire or explosion. – The accidents or incidents caused or that could potentially happen due to the presence of chemical agents in the work place. • Exposure to several hazardous chemical agents: – Where the exposure is to several hazardous chemical agents, the effects of the risks presented by all chemicals together is based on a formula which is not applied where scientific data allow a better evaluation of the exposure (BE). – The sum of relations of concentrations to the limit values of each of the hazardous chemical agents shall not exceed 1 (BU). • An assessment of the risks to the safety and health of workers shall include only the highest exposure limit values or biological limits (SK).	exposure, but also describe safety requirements, OELs, measures if OEL is higher than required, as well as the results of the measurements of the carcinogenic concentration at workplace (LV). • Restrictions over the areas in which CMs may be used, i.e. not in primary or high schools, in universities only where a special authorisation has been granted (SK).
Note: Recurring measures shall be understood as measures which are common to at least two EU Member States.		

X3.5.2 Risk management measures

A majority of EU Member States have implemented a series of additional requirements for the main risk management measures, in comparison to those set out in the CAD and CMD. Based on the available information, there are measures which appear to be recurring among several EU Member States, while others are unique to a particular EU Member States.

The list hereunder is not exhaustive as such a compilation would require the analysis of each and every measure taken by EU Member States in view of implementing provisions related the CAD and CMD.

Prior to providing a list of such measure, the following table offers a reminder of the differences between the CAD and the CMD with regard to risk management measures through prevention/reduction of occupational risks, following the performance of a risk assessment.

Table X3-5: Differences between the CAD and CMD (RMMs)		
	Chemicals at Work Directive (CAD)	**Carcinogens and Mutagens Directive (CMD)**
RMMs	If 'slight risk' is identified (because of quantities of chemical present): • Implement list of RMM to eliminate/reduce the risk (Art.5.2&5.4) If risk is identified (>'slight risk'): • Comply with hierarchy for further RMM: 1) Substitution of the chemical: 2) Reduction of the risk to a min. by applying protection and prevention measures in the following order: – designing processes, controls, using adequate equipment; – collective protection measures at the source of the risk; – individual protective measures; – …(Art.6.2)	• Reduce the use of & replace the CM substances at the place of work (substitution), if technically possible (Art.4.1) If risk is identified: • Prevent workers exposure (Art.5.1) • Provide information to the competent authorities (Art.6) • Restrict access to areas with CM substances (Art.9) If replacement is impossible: • Comply with hierarchy for RMM: 1) Closed system; 2) Reduction of the level of exposure as low as technically possible (Art.5.2&5.3) • Implement mandatory RMM list (all provided in Art.5.5)

In addition to the provisions in the CAD and CMD, some Member States have adopted further requirements than those in the CAD and CMD, see table below.

Table X3-6: National requirements that go beyond those set out in the CAD (RMMs)		
	Chemicals at Work Directive (CAD) Art. 5-6	**Carcinogens and Mutagens Directive (CMD) Art. 4-5**
Recurring		• Limitations of the extent and duration of the exposure (AT, NL) • Involving the national competent authority: – Prior authorization of competent authority to handle certain substances (SE) – Prior notification to inspection authority and the Institute for Health and Safety at Work 30 days before commencing the products and use of CMs (HR).
Individual	• Packages having a presentation or denomination used for food, feed, medications and cosmetics are not be used for hazardous substances and mixtures (BE). • Employers have a duty of care and information and must possess necessary expertise and knowledge	• Prohibition of the use of CMR substances where an equivalent result may be reached with a non-dangerous agents (not only the reduction) (AT). • Permanent control areas should be created for CMRs (CZ). • Suggestion of candidates for substitution (DE).

Table X3-6: National requirements that go beyond those set out in the CAD (RMMs)		
	Chemicals at Work Directive (CAD) Art. 5-6	**Carcinogens and Mutagens Directive (CMD) Art. 4-5**
	to handle chemical agents and to react in case of risks (FI). • When assigning an employee to work with chemical substances and preparations, account must be taken of the professional education, experience, training and level of preparedness of the employee in the field of labour protection (LV). • In listed circumstances the employer must proceed to measurements of exposure or analysis of the substances mixed or used (BE). • Employers shall take preventive and protective measures so that an occupational exposure limit value is not exceeded; in the event, where an occupational exposure limit value has been exceeded, the employer shall immediately take measures (CY). • Additional record keeping obligations when a regular inspection of the environment takes place (GD). • Additional prohibitions: workers cannot be employed in workplaces where the concentration of hazardous substances in the ambient air exceeds specific limit values; employers cannot be exposed to hormone agents and antibiotics, moreover, cannot be employed in workplaces where asphyxia could occur due to the high concentration of certain substances (HU).	• Environmental legislation requires to communicate the reduction scheme and phasing out of substances to the environmental authority, where the substances falls under the Solvent Directive (RO). • Employers must apply closed systems if employees are subject to high risks of exposure through inhalation (DE). • Detailed requirements for the evacuation, extraction and ventilation of CMRs at source by applying specific techniques based on technical feasibility, maximizing the effectiveness and efficiency of the evacuation, extraction and ventilation systems as well as providing a warning system to alert any failures of such systems (FR). • The applied prevention and protection measures must be adapted to the specific situation (IT). • Additional measures to be taken including: (NL) – a local exhaust of air, supplemented, if necessary, by adequate ventilation and supply of uncontaminated air; – demolition and maintenance work shall be made by or under the constant supervision of a person in possession a certificate of competence for the type of work being performed. • Hazardous chemicals should be handled in such a way that those no directly affected by the work are also protected against the risk. To that effect, a time and place for handling such substances should be chosen (SE). • The exposure of workers should be reduced to the lowest level according to technical scientific knowledge (HU). • Additional requirements and details for measurements such as: measurement procedures shall be carried out only through sufficiently skilled and equipped persons, adapted to the agent, the limit value of the agent and to the atmosphere at the work station (AT). • Workspaces should be cleaned at least one a weak and in any case when necessary (HU).
Note: Recurring measures shall be understood as measures which are common to at least two EU Member States.		

X3.5.3 Other measures

The majority of EU Member States have implemented a series of additional requirements for other risk management measures, in comparison to those set out in the CAD and CMD. Based on the available information, there are measures which appear to be recurring among several EU Member States, while others are unique to a particular EU Member States.

The list hereunder is not exhaustive as such a compilation would require the analysis of each and every measure taken by EU Member States in view of implementing provisions related the CAD and CMD.

Prior to providing a list of such measure, the following table offers a reminder of the differences between the CAD and the CMD with regard to other risk management measures which are provided.

Table X3-7: Differences between the CAD and CMD (other measures)

	Chemicals at Work Directive (CAD)	Carcinogens and Mutagens Directive (CMD)
Accidents, incidents and emergencies **Called 'unforeseen exposure in CMD'**	• If risk is identified (>'slight risk'): – Prepare action plans to deal with accidents, incidents and emergencies (Art.7.1) – In the event of accident, incident or emergency: ✓ Mitigate the effects and inform the workers (Art.7.2) ✓ Provide PEE to workers in the affected areas (Art.7.3) ✓ Provide warnings & communicate on the increased risk for health and safety (Art.7.4) • Provide information on emergency arrangements: list (Art.7.5)	• Inform workers (Art.7.1) • Permit access only to workers who are essential to carry the repairs and other necessary work, equipped with PPE (Art.7.2)
Information and training[198]	• Provide workers and/or their representatives with relevant training, data and information; list applying in addition to Framework Regulation (Art.8)	• Provide workers and/or their representatives with relevant training, data and information; list provided (Art.11&12) • Consultation of workers for the implementation of CMD (Art.13)
Health surveillance (HS)[199]	• If risk is identified (>'slight risk'): – Cases where HS is required: based on exposure, likelihood of disease, etc.); compulsory if BVL (Art.10.1) – Techniques for detection of diseases (Art.10.1) – Health and exposure records (Art.10.3) • If disease of a worker information, review safety	• If risk is identified: – For workers at risk based on the risk assessment → compulsory HS in compliance with national laws (Art.14.1) – Surveillance before and after exposure (Art.14.2) – Health and exposure records (Art.14.4) – If disease/abnormality of a worker → doctor or other authority may require HS for other workers

198 Information and training is a general requirement of the Framework Directive (Art.10 and 12)

199 The health surveillance is a general requirement of the Framework Directive (Art.14)

Table X3-7: Differences between the CAD and CMD (other measures)		
	Chemicals at Work Directive (CAD)	Carcinogens and Mutagens Directive (CMD)
	assessment, search advise, continue HS (Art.10.4)	
Hygiene and individual protection	N/A	• Comply with list in Article 10: ensure that no eating, drinking, smoking in C&R areas; protective clothing; storage and whishing facilities; etc.

In addition to the provisions in the CAD and CMD, some Member States have adopted further requirements than those in the CAD and CMD, see the tables below.

Table X3-8: National requirements that go beyond those set out in the CAD (other measures)		
	Recurring	Individual
Arrangements to deal with accidents, incidents and emergencies (art.7)	• Access to the work place where dangerous chemical agents are used is limited to those persons assigned to work there. Employers must post signs that prohibit entry to unauthorized persons and that identify the health risks of emissions of dangerous chemical agents, including through accidents (FR, LT) • Establishment of emergency plans to set out the procedures to be implemented in case of an accidents, incident or emergency and detailed rules on such plans (BE, FI) • Employers shall prevent workers from eating, drinking and smoking in the workplace where they are exposed to dangerous chemicals (FR, LT, AT, NL)	• Application of CMD requirements for unforeseen exposure to the arrangement to deal with accidents, incidents and emergencies (CZ). • Setting up a controlled area (CZ). • Workers authorized in the affected zone must receive appropriate clothes and respiratory protective equipment and security equipment which they must use as long as the risk persists, the situation may not be permanent (BE). • Employers must immediately take measures to reduce the effects and inform the workers. To re-establish a normal situation the employer must implement adequate measures to fix the situation as soon as possible; only workers which are indispensable for the reparations and other necessary work are authorized to work in the affected zone (BE). • Persons who are not protected are not authorized to stay in the affected zone (BE). • Employers must provide alarm systems and other communication systems required to signal a high risk for security and health (BE). • Employers must provide necessary installations to avoid the effects of the emission of chemical agents (BE). • Several documents must be provided to the internal and external services that must intervene (BE). • Measurements should be taken if it can be excepted that the chemical substance or dust will be present in the workplace even after the conclusion of all measures to address the unforeseen event (CZ). • Workplaces where an unforeseen event can cause a release of a volatile chemical element at a level which can cause a harm to health, there must be emergency ventilation, which

Table X3-8: National requirements that go beyond those set out in the CAD (other measures)		
	Recurring	Individual
		can be easily switched on before entering the workplace (CZ). • Additional detailed preventive measures (training of workers, organization with external services such as firemen) are to be planned by employers (ES). • Immediately inform all the workers, not only who may be exposed to danger, but also other workers in the undertaking about the danger and instruct them on the measures which will be taken to protect life and health of the workers and on actions to be taken by the workers themselves (LT). • Take all necessary measures to suspend work (LT). • Immediately inform relevant internal and external emergency services (LT). • Organise provision of first aid to the injured, as well as the evacuation of workers (LT).
Information and training of workers (art.8)		• Application of the CMD requirements (CZ). • Written health and safety rules must be established and must be accessible to the workers at the workplace and must contain information on the properties of the substance, health and safety, first aid and emergency guidelines which had been consulted with public authorities (CZ). • Employer is obliged to provide instruction manuals in written form and to inform the employees orally of all hazards and necessary protection measures on the basis of the instruction manuals. If necessary, a physician must take part in the oral instructions (DE). • Employers establish a notice board for each workstation exposed to dangerous chemical agents. This notice board is to be updated when needed and serves to inform workers of the risk of exposure and appropriate measures for avoiding risk. Additional information includes hygiene rule, and instructions related to the use of individual and collective protective equipment (FR). • Employers must: provide their employees with a possibility of participating in the determination of the potential dangers of chemical substances (risk assessment); and provide medical advice to employees if necessary (HU). • Employers shall also provide information on measures in case of: (SK) – unforseen situation;

Table X3-8: National requirements that go beyond those set out in the CAD (other measures)		
	Recurring	**Individual**
		– on the outcomes of measuring hazardous chemical agents in occupational ambience and in biological material in relation to the maximum occupational exposure limit values and biological limit values; – on the occurence of occupational diseases and their reasons. • Workers shall be informed on possibilities of medical surveillance too (SK). • Producers and suppliers must provide all information on hazardous chemical agents, if requested so by the employers (SL).
Note: Recurring measures shall be understood as measures which are common to at least two EU Member States.		

Table X3-9: National requirements that go beyond those set out in the CMD (other measures)		
	Recurring	**Individual**
Unforeseen exposure (art. 7)	• Alarm systems should be set up (HU, NL)	• The work in the contaminated zone should be terminated until normal conditions are restored (BU). • Communication: – Workers should be informed not only when accidents occur in reality but also where there is a high probability that an accident could occur in the future (EE). – Workers should be informed 'immediately' (GD). – The supervisory body shall be informed immediately (IT). – Employers shall communicate the measures that are taken to the supervisory body (IT). • The elimination of CMR shall be done in such a way that it does not create new risks in the work place or working environment (FR). • Workers should be sent to medical and cytogenetical examinations (HU). • The place where the exposure happened should be demarcated and indicted by means of a sign (HU). • It is the duty of all employees to wear personal protective equipment provided by the employer (IT). • The suitable measures shall be taken 'as soon as possible' (IT). • Coordinate the emergency response with one or more designated employee(s), which will have received the necessary training and

Table X3-9: National requirements that go beyond those set out in the CMD (other measures)		
	Recurring	Individual
		equipment to be able to respond effectively, responsible for such emergency response, including the provision of first aid; taking all necessary measure to limit the consequences of the accident and any fire fighting, switch on the emergency alarm and evacuate all employees and other persons in the business or establishment (NL). • Specific measures of prevention of unforeseen exposure such as to avoid the presence of hazardous inflammable substances or of chemically unstable substances in the workplace unless not possible with regards to the nature of the work; to ensure that no ignition sources are present which can cause fires and explosions, or adverse conditions leading to chemical instability which could cause harmful physical effects; to reduce the harmful effects on health and safety of workers in the event of fire or explosion due to the ignition of flammable substances, or harmful physical effects arising from accidents caused by chemically unstable substances or mixtures of substances reduced. The measures shall be tailored to the type of activities, including storage, handling and confinment of incompatible hazardous substances, and measures to protect workers against the dangers of physicochemical properties of hazardous substances (NL). • The risk assessment shall form the basis of the employer's decision concerning which handling and safety instructions are to be given, and it should also indicate the preparedness and the first-aid routines that are needed and should exist to protect workers in the events of accidents, incidents or emergencies related to the occurrence of hazardous chemical substances (SE). • The employer must carry out exposure measurements when there is a reason to suspect that an occupational exposure limit has been exceeded. The employer must inform the employee about the results of the measurements and give the employee access to the documentation (SE).
Foreseen exposure (art. 8)		• Employer is obliged to consult the employees in all questions related to the protection of safety and health at work (AT). • Employers must consult with a specialist in occupational health to determine which measures are necessary to reduce the duration

Table X3-9: National requirements that go beyond those set out in the CMD (other measures)		
	Recurring	**Individual**
		of workers' exposure to CMR agents to the minimum possible and to ensure workers' protection while they are engaged in activities entailing foreseen increases in exposure. The employer must consult an occupational doctor and the economic and social comity prior to determining the measures that must be taken (FR). • Reduction of the exposure to concrete exposure limit values (HU). • It is the duty of all employees to wear personal protective equipment provided by the employer (IT). • Preventive plans to be written down in a collective agreement or in a written arrangement agreed by the employer and workers representatives (NL). • The areas are referred to as a 'monitored zone' and as such shall be demarcated, clearly and visibly marked. These zones are appointed by public health authority upon proposal of an employer. In other words – it is not upon subjective assessment of an employer to demarcate such areas (SK).
Access to risk area (art. 9)		• Only workers who have received adequate training may access the risk area (BE). • Only persons in good physical and mental condition, with a basic knowledge and ability to identify associated hazards and preventive actions may be allowed to perform the work (NL). • The areas are referred to as a 'monitored zone' and as such shall be demarcated, clearly and visibly marked. These zones are appointed by public health authority upon proposal of an employer. In other words – it is not upon subjective assessment of an employer to demarcate such areas (SK).
Hygiene and individual protection (art. 10)	• Banning the activities of eating, drinking and smoking in the areas where there is a risk of contamination (AT, NL, CZ, NL) • Forbidding/banning the use of cosmetics in the areas where there is a risk of contamination (AT, NL, IT, SE) • Not allowed to take drugs, bring drinks, food and tobacco into the areas (AT, NL). • Forbidding workers to exit the establishment with their work clothes/take them home (FR,	• Food, drinks and smoking in areas where here is a risk of contamination: – obligation to visibly warn workers about the ban on eating, drinking and smoking where there is a risk of contamination and enforce it. A separate area has to be designated for eating and drinking (CZ). – not allowed to conserve human food or use mouth pipette (IT). – food, drinks cannot be prepared or stored if there is a risk of ill-health (SE). • Washing facilities:

Table X3-9: National requirements that go beyond those set out in the CMD (other measures)		
	Recurring	**Individual**
	ES, LV) • Employees working with hazardous agents shall be obliged to wash themselves carefully inter alia before drinking, eating or smoking or after work (NL). • Employees working with hazardous agents shall be obliged to wash themselves carefully inter alia before drinking, eating or smoking or after work (AT, NL). • Employers have the obligations to maintain and clean protective equipment, assess its condition and immediately rectify any defects (AT, NL). • Employees, who are ill, or employees with an injured skin, which would favor the infection through skin, shall not be allowed to work in these areas (AT, NL). • The washing facilities should have efficient hygienic, running water and, if possible, warm water, soap and adequate drying facilities (AT, NL).	– employers must provide 1 shower per group of 3 workers who simultaneously finish their work, with hot and cold water (BE). – workers must be provided within the working day, ten minutes for personal hygiene before lunch and ten minutes before leaving work (ES). – employers must provide their workers with hygienic detergents and decontaminants of appropriate quantity and quality (HU). • Protective equipment: – Workers must not exit the establishment with the individual protective equipment (FR). – the work shall be planned and conducted in such a way that the protective equipment can be used in an effective manner with the least possible inconvenience to the user (SE). – protective equipment shall be always cleaned before and after each use, i.e. not only 'if possible' (SK). • Clothing: – work clothes should be checked and cleaned before and after each use (CZ). – the employer is responsible for the cleaning and decontamination of working clothes (ES). – working clothes are to be washed by suitable companies and transported in closed containers and adequately labelled (ES). – it shall be possible to store work clothing and private clothing separately if there is a risk of ill-health or discomfort due to the transmission of a health-endangering substance (SE). • In case of outdoor works, the employees must have a place to change their clothes (tempered dressing room) and a resting room. The exposure concentration at these places cannot exceed the emission limits (without such limits, the maximum concentration limits must be the same as in the closest town) (HU). • Employers are obliged to provide relaxation rooms (SK). • Conditions are set if the up-keeping of protective equipment is ensured by an external actor from the company (FR).

Information and training of workers (art. 11) & Information for workers (art. 12)	• Training to take place within a specific deadline, at least every year for example (BE, LV)	• Form of information and/or instructions: – operating manuals or instructions shall be handed out (AT). – In the context of training, each worker receives an individual note in which all information and instructions should be included (BE). – As long as a workers are in a risk-prone zone, they shall receive adequate training and a copy of the individual note, at an interval of maximum one year (BE). – Information should be provided in written (HU). – the information and training shall be in provided in the mother tongue of the employee, if the employee is not skilled enough in German or list the cases, when training is to be delivered in any case (AT). • Prohibition of an employer to request a worker to start working if he is not instructed about safety at work (LT). • Workers may refuse working (the work must be suspended) if: the worker has not been trained in a safe work; the workers are not provided with appropriate collective and (or) personal protective equipment; there are other cases when the working environment is hazardous and/or dangerous to health or life (LT). • The employer is obliged to consult employees in all questions related to the protection of safety and health at work (AT). • Upon request of the official in charge of surveillance, the employer must provide appropriate information on: (BE) – Activities/industrial procedures that have been set up, including the reasons for which carcinogenic, mutagenic or reprotoxic agents are used; – Results of his research; – Quantities of substances/preparations with CMR agents that are made or used; – Number of exposed workers; – Nature and degree of exposure; – Case of substitution. • The information and the formation are given prior to work commencing and shall be renewed almost every five years, and following changes in the manufacturing process that are important in relation to the nature or degree of risks (IT). • Right of the worker to have access to the risk assessment documents and for employees concerned by risks, to be informed on the

Table X3-9: National requirements that go beyond those set out in the CMD (other measures)		
	Recurring	Individual
		results of the risk assessment and subsequent decisions (SE). • Information must be provided to workers and workers representatives, on the cause of any accidental exposure to carcinogens and mutagens and on the measures adopted or that should have been adopted to remediate this accidental exposure (ES). • In case exposure to carcinogens occurs due to human activities, training must be hold immediately and the programme of the training must be adjusted to the new dangers caused by the human activities (HU).
Record-keeping (art. 15)		• The employer keeps a register of works, the performance of which makes it necessary to keep in contact with chemical substances, their mixtures, agents or technological processes of carcinogenic or mutagenic effects, containing certain listed data (PL).
Note: Recurring measures shall be understood as measures which are common to at least two EU Member States.		

X3.6 Country summaries – EU Member States

X3.6.1 Austria

At the federal level, the main legislation transposing both the CAD and the CMD, is the Act on the Protection of Safety and Health at Work of 1994 (ASchG). It provides general principles on the prevention of risks at work and applies to 'dangerous substances'. Most obligations are correctly transposed but the ASchG also extends certain CMD obligations to 'dangerous substances', therefore covering more than CMRs and rendering the requirements for reprotoxins, generally equivalent to the CMD. The ASchG also details some provisions and is more stringent for the substitution requirement of CMRs.

We note that separate legislation is implemented to cover civil servants and rural work.[200] In that respect, "the Constitution attributes to the Länder the legislative power for the implementation legislation for rural work and the legislation for the work of civil servants of the Länder and the municipalities as well as the executive power thereof. More than 60 legislative acts are providing the rules on safety and health". [201] However, for this report, the analysis of the transposition is limited to the federal level.

[200] Act on the Protection of Federal Civil Servants, Bundesgesetz über Sicherheit und Gesundheitsschutz der in Dienststellen des Bundes beschäftigten Bediensteten (Bundes-Bedienstetenschutzgesetz - B-BSG), BGBl. I Nr. 70/1999 as amended by BGBl. Nr. 153/2009; Act on Rural Work, Bundesgesetz betreffend die Grundsätze für die Regelung des Arbeitsrechts in der Land und Fortwirtschaft (Landarbeitsgesetz – LAG), BGBl. Nr. 612/1986 as amended by BGBl. I Nr. 37/2011.

[201] RPA, Milieu, Report 2012, p.3.

X3.6.2 Belgium

Both the CAD and the CMD were integrated into the Belgian Code of Wellbeing (BCW) in 2017 within separate titles. The title implementing the CMD was extended to include reproductive toxins and transposes the CMD's provisions, with some additional obligations.

The BCW clarifies the hierarchy between the measures under the CMD and provides that (i) the substitution is required if the risk assessment reveals a risk for the health and safety of the workers, and (ii) the limitation of the exposure is required anytime where a CMR substance is used, independently from any risk having to be detected in a risk assessment.

An important justification to their choice of method was to enhance coherence with other related EU legislation where CMRs are mentioned together.

X3.6.3 Bulgaria

In Bulgaria, the CAD and CMD are transposed into existing national legislation adopted and enforced before Bulgaria joined the EU.

The main legislation transposing the Framework Directive is the Law on Health and Safety at Work (December 1997), which also partially transposed the CAD in addition to the Ordinance N°13 of 2003 on the protection of workers from risks related to exposure to chemical agents at work. The CMD however, is only transposed through Ordinance N°10 of 26 September 2003 on the protection of workers from risks related to the exposure to carcinogens and mutagens at work. Specificities for risk assessments and examinations of workers, among others, are detailed in Ordinance N°5 of 11 May 1999 on the order, manner and periodicity of conducting a risk assessment, and Ordinance N°3 of 28 February 1987 on compulsory preliminary and periodical medical examinations of the workers.

Based on the reports to which we had access, Bulgaria has fully implemented the CAD and CMD without extending their scopes. Most provisions are limited to what the CAD and CMD set out.

X3.6.4 Croatia

Croatia transposes the CAD and CMD through two separate acts. The Croatian Regulation on the protection of workers against the risk of exposure to dangerous chemicals at work transposes the CAD and the Regulation on the protection of workers against the risk of exposure to carcinogens and/or mutagens transposes the CMD. A separate legislative act only regulating substances toxic for reproduction has not been issued in Croatia.

The measures set out in both acts correspond to the legal requirements of both the CAD and the CMD with some additional requirements when it comes to commencing an activity which involves CMs

X3.6.5 Cyprus

The legal system in Cyprus is based on national laws and regulations. EU acts pertaining to health and safety at work have been transposed through multiple laws brought together under the heading 'The Safety and Health at Work Laws of 1996 to 2011' (SHL). Therefore, the Framework Directive is said to be transposed by one main law whereas institutional aspects are covered by separate Regulations. The CAD and the CMD have been transposed in individual single acts, in the form of Regulations, respectively The Safety and Health at Work (Chemical Agents) Regulations of 2001 and The Safety and Health at Work (Carcinogenic and Mutagenic Agents) Regulations of 2001, with their relevant

amending Regulations. These Regulations constitute secondary legislation, issued under legal authorization provided by article 38 of the Laws on Safety and Health of 1996 and 2001.

With regard to the transposition of the CAD and the CMD, Cyprus has followed a word-by-word approach and has not included reprotoxins under the CM Regulations. It does however specify that obligations imposed under the Regulations extend, as far as is reasonably practicable, to other persons who may have been affected by the employer's business and apply to self-employed persons in the same manner as they apply to employers and persons at work

X3.6.6 Czech Republic

The CAD and the CMD are implemented through several measures. The general requirements on occupational health protection law are given in the Labor Code (Law 262/2006) and in the Public Health Law (Law 258/2000). Next, the legal act which transposes the CAD and the CMD is Law 309/2006, which applies to all dangerous chemical substances. However, the detailed requirements of both Directives are found in the Government Decree 361/2007, determining the conditions for the protection of health at work. Decree 361/2007 explicitly refers to reprotoxins for which a specific definition is provided. Additionally, the Czech Republic has a law on chemical substances and preparations which sets out the procedures for determining which substances are reprotoxic, i.e. Law 365/2003.[202]

These measures are completed by the Government Decree 432/2003, laying down conditions for job categories, limit values of biological exposure tests, sampling conditions of biological material for biological exposure tests and requirements for reporting work with asbestos and biological agents.[203]

Additional requirements are notably provided for in the areas of unforeseen exposure and information of workers. These requirements are applicable for dangerous chemical substances and not only CMRs.[204]

X3.6.7 Denmark

In 2015, Denmark issued two new Decrees transposing the requirements of the CAD and the CMD, respectively, the Decree on work with substances and materials No. 1793 of 18 December 2015 and the Decree on measures to prevent cancer risk in work with substances and materials No. 1795 of 18/12/2015.[205] The provisions of the CMD have not been extended to cover reprotoxins and two measures faithfully transpose the provisions of both Directives.

X3.6.8 Estonia

Most provisions of the CAD and the CMD are transposed in individual implementing regulations. Regulation of the Government No. 105 of 20.03.2001 on Occupational health and safety requirements for using hazardous chemicals and materials containing the latter, transposes the CAD, while Regulation of the Government No. 308 of 15.12.2005 on Requirements for using carcinogenic and mutagenic substances at workplace, transposes the CMD. However, some aspects of the Directives

[202] RPA, Milieu Report, 2012, p.61.
[203] Amended by Decree 107/2013.
[204] RPA, Milieu Report, 2012, p.69.
[205] Replacing BEK292/2001: Ministerial Order No 292 of 26 April 2001 on working with substances and preparations (chemical agents) and BEK908/2005: Ministerial Order No 908 of 27 September 2005 on measures to prevent the risk of cancer due to work with substances and preparations.

are regulated by the national legislation transposing the Framework Directive, the Occupation Health and Safety Act (TTOS), or 'horizontal' implementing acts, which are secondary legislation.

Regulation No.105, transposing the CAD has a particular flaw. The Regulation applies to activities involving hazardous substances or the materials containing the latter, validated under the Regulation No. 59 on the Confirmation of the list of hazardous substances of the Minister of Social Affairs of 30 November 1998. The flaw is caused by the fact that the regulation of the Minister of Social Affairs was annulled in 2004 and was not replaced by any new regulation. Conclusively, Regulation of the Government No. 105 does not have a scope and cannot be applied.

With regard to the CMD requirements, issues concerning health surveillance, information and training of workers and the definitions of carcinogens and mutagens are found in other measures. Under the CAD, rules on health surveillance, consultation of workers, the general obligation to conduct a risk assessment, questions concerning information and training as well as preventive and protection services, among others, are also found in separate legislation than the Regulation No.105.

Generally speaking, the obligations of both Directives have been faithfully transposed and reprotoxic substances have not received any special attention in policy level. There is no political debate on the issue and society does not have awareness on risks related with reprotoxic substances.

X3.6.9 Finland

The implementation of the CAD is transposed into the Government Decree on chemical agents at work No. 715/2001, recently incorporated into the Decree on concentrations known to be hazardous No. 1214/2016. The implementation of the CMD remains in the Government Decree on the elimination of cancer risk in connection with work No. 716/2001 (also applicable to mutagens). The transpositions generally follow the requirements set out in the CAD and the CMD.

Regarding reprotoxins, Finland has a specific Government Decree on agents causing risk to reproductive health in work and the prevention of such risk No. 603/2015. This Decree notably covers reprotoxins of Cat. 2 and sets out requirements which amount to a combination of those under the CAD and the CMD. However, all the requirements set out in the Decree are also applicable to carcinogens and mutagens but specific requirements limited to carcinogens and mutagens exists as well.

X3.6.10 France

France transposes the CAD and CMD in the French Labor Code ('FLC'). The main provisions are laid out in the Regulatory Part of the FCL, in Part IV 'Health and Safety at work', Book IV 'Prevention of exposure risks', Title I 'Chemical risks', Chapter II 'Prevention measures against chemicals risks'.

Although both Directives have been transposed into a single legislation, separate sections are provided for the implementation of the CAD and CMD. The FLC includes an explicit reference to reprotoxic substances (categories 1A and 1B) in the provisions established for the implementation for the CMD. In doing so, the Code goes beyond the requirements of the CMD. However, there are some points that are not clear in the French legislation notably with regard to the need of a risk to be identified in the risk assessment for substitution to be triggered.

X3.6.11 Germany

The legal landscape in Germany is quite complex and involves multiple authorities and sets of rules since the competences on occupational health and safety are split between the Federal Parliament, the Federal Ministry and its institutions, but also the authorities of the 16 Federal States, the Länder with their ministries and labour inspectorates. The Federal layer has the legislative competence, while the Federal States control their fulfilment in their territory. For purposes of this report, we have focused on the Federal, i.e. national level, but it must be noted that the situation is more complex in practice.

both the CMD and CAD have been transposed into German law through the 2010 Hazardous Substance Ordinance, generally applicable to 'hazardous substances'. Additional technical rules produced by the Committee on Dangerous Substance (AGS) regulate the use of reproductive toxins through the establishment of lists of substances that it considers CMR, either in addition to what the CLP sets out or in deviation, and lists of carcinogenic activities.[206]

The Hazardous Substances Ordinance has a multi-tiered risk management system for all substances that fall under the CAD and CMD. If occupational exposure is identified, basic obligations and general protection measures must be complied with. If these measures do not rule out the risk of oral, dermal or inhalation exposure, employers must take additional measures. Moreover, if occupational activities are carried out that involve CMRs, employers must take further protection measures.

The 2010 Hazardous Substance Ordinance has extended certain CMD provisions too all substances for which the risk assessment has revealed a risk, therefore including reprotoxins. This is notably the case regarding substitution, which is a general requirement. However, there are also certain CMD provisions which have either deliberately been extended to reprotoxins (e.g. demarcation or the assessment of exposure by measurements), or deliberately not been extended to reprotoxins (e.g. record keeping for 40 years or health surveillance).[207] The 2010 Hazardous Substance Ordinance also provides for exemptions,[208] and is supplemented by technical rules on hazardous substances which may be followed on a voluntary basis, the compliance of which creates the assumption that the employer conforms with the Ordinance.

Consequently, reprotoxins are included under the general scope of the Ordinance and under the specific measures laid out for CMRs.

X3.6.12 Greece

The CAD is mainly transposed through the Presidential Decree 338/01 on the protection of health and safety of workers at work from risks related to chemical agents. The scope of the relevant Greek legislation coincides with the scope of the CAD and all definitions provided by the Directive are literally transposed in the Presidential Decree. The provisions regarding specific protection and prevention measures elaborate further on monitoring and control.

Greece did not transpose the CMD per se but instead, the Presidential Decree 399/1994 on the Protection of workers from the risks related to exposure to carcinogens and mutagens at work transposes the previous Directive 90/394/EEC. The Presidential Decree covers CMs, as defined by the CMD, the provisions of which are almost literally transposed. Additional requirements are limited to

[206] RPA, Milieu Report, 2012, p.131.
[207] Milieu/RPA Report, 2012, p.132 ; Art. 10 of the 2010 Hazardous Substance Ordinance.
[208] *Ibid.*

having a written assessment of the existing risks at work and 'immediately' informing workers in situations of unforeseen exposure.

Exposure of workers to reprotoxic substances constitutes a low priority issue in the Greek political and social agenda. Consequently, there is no research, data, or guidance material focused on the risks from the exposure to reprotoxic substances.

X3.6.13 Hungary

The provisions of the CAD are adequately transposed through the Ministerial Decree 25/2000 (IX.30.) on the Chemical Safety of Workplaces, Act XCII of 1993 on Labour Protection and Act XXV of 2000 on Chemical Safety. The Labour Protection Act sets the general obligations of employers, while the Chemical Safety Act provides the main obligations of employers with regard to chemical agents and serves as the legal basis for adopting the Ministerial Decree. Additional requirements are imposed for specific protection and prevention measures and information to workers.

The CMD is implemented through in the Ministerial Decree[209] 26/2000 (IX.30) on protection against carcinogenic substances of occupational origin and on the prevention of health damage caused by such substances. The scope of the Ministerial Decree is limited to CM substances only, the definitions of which essentially refer back to Appendixes 1 to 4 of Annex XVII REACH. Substances and preparations can also be considered as carcinogens when they are released by processes referred to in Annex II of the Ministerial Decree (e.g. production of auramine). Additional requirements and details are established with regard to conducting a risk assessment, the prevention and reduction of risk, unforeseen and foreseen exposure, hygiene and individual protection and information for workers.

X3.6.14 Ireland

In Ireland, the Safety, Health and Welfare at Work Act 2005 (No. 10 of 2005) sets down the general requirements for the management of health and safety in the workplace. This act is supplemented by the Safety, Health and Welfare at Work (General Applications) Regulations 2007 (S.I. No 299 of 2007).

The CAD is implemented through the Safety, Health and Welfare at Work (Chemical Agents) Regulations 2001 (S.I. No.619/2001) which generally correctly transposes the legal requirements from the CAD. It must however be noted that with regard to risk management measures, there appears to be no requirement to implement substitution prior to other listed measures.

In 2012, the CMD was faithfully implemented through the Safety, Health and Welfare at Work (Carcinogens) Regulations 2001 (S.I. No. 78 of 2001) by globally replicating the provisions of the CMD.

However, in 2015, amendments were brought to both sets of Regulations. According to the 2017 Report, the CMD is now indirectly implemented through the Safety, Health and Welfare at Work (Carcinogens) (Amendment) Regulations 2015 (S.I. No. 622/2015).

Limited information was provided on the content of such amendments, preventing this report from producing a more accurate summary of the current legal situation in Ireland Nonetheless, based on the 2017 Report on Ireland, it appears that the essence of the legal requirements have not been changed since the prior 2012 Report. This allows for certain information on Ireland to be included within the Report.

[209] Decree adopted by the Ministry of Health.

X3.6.15 Italy

Italy has transposed the CAD and CMD into the Legislative Decree N°81/2008 in which Title IX regarding hazardous substances is sub-divided into separate sections for chemical agents and for CMs. The implementation of the CMD provisions was not extended to reprotoxins, which remain covered under the national legislation implementing the CAD provisions.

The obligations of each section generally correspond to those of the CAD and CMD with some measures being more detailed. Italian legislation establishes additional requirements when determining risk assessment and employer responsibilities for prevention and protection.

X3.6.16 Latvia

The CAD is transposed into national legislation by Regulations of the Cabinet of Ministers No 325/2007 on Labour protection requirements when coming in contact with chemical substances at workplaces. The latter applies to workplaces where an employee is or may be exposed to the effect of such chemical substances and chemical preparations. Certain CAD provisions were not entirely transposed, notably those relating to specific protection and prevention measures, arrangement to deal with accidents, incidents and emergencies, and the information and training of workers.

The CMD is transposed into Latvian legislation by Regulations of the Cabinet of Ministers No 803/2008 on Labour protection requirements when coming in contact with carcinogenic substances at workplaces. Latvia's national legislation implementing the CMD does not cover reprotoxic substances. Furthermore, while the provisions set out more stringent requirements for the risk assessment, other provisions are not/not fully transposed such as the access to risk areas, details over caring for protective equipment and obligations regarding the information and training of workers.

X3.6.17 Lithuania

The Republic of Lithuania's Law on Safety and Health at Work, as last amended by the Law No XI-1202 of 2 December 2010 sets out basic requirements on the protection of workers from exposure to dangerous chemical substances and preparations. This general legislation is complemented by Order 97/406 which approved Regulations on the Protection of Workers from Impact of Exposure to Carcinogens and Mutagens at Work and Regulations on Protection of Workers from Chemical Agents at Work. Additionally, the Order on Lithuanian hygiene HN 23:2001 on limit values for the professional effects of chemical substances, general requirements for measurement and impact assessment of 1 November 2011 sets out obligations reflected in its title.

The main legislation implementing the CAD is the Order 97/406 where it approved Regulations on Protection of Workers from Chemical Agents at Work and the Lithuanian Order on Lithuanian Hygiene rates HN 23:2011. The general scope is equivalent to the CAD's and most provisions are literally transposed.

The provisions reflecting those of the CMD were almost all literally transposed and do not extended to reprotoxic substances. The legislation sets out a few additional rights and obligations with regard to the information and training of workers. However, certain requirements from the CMD have been inserted into the Regulations applicable to all chemical agents in the article pertaining to specific protection and prevention measures.

X3.6.18 Luxembourg

In 2016, Luxembourg Luxembourg issued two new legal acts regarding risks of exposure to chemical agents in the workplace: the Grand Ducal Regulation of 14 November 2016 concerning the protection of the health and safety of workers against the risks associated with chemical agents in the workplace and the Grand Ducal Regulation of 14 November 2016 concerning the protection of the health and safety of workers against the risks associated with carcinogenic and mutagenic agents in the workplace. The French versions of these measures cover workers under the term 'salarié' which may imply that only employees are covered.

The legislation is limited to the respective implementations of the CAD and CMD without setting out additional requirements. Reproductive toxins are not covered under the national legislation implementing the CMD.

X3.6.19 Malta

Malta transposed the CAD and CMD through existing national legislation enacted prior to their accession to the EU, in 2004. The authority legislation is the Occupational Health and Safety Authority Act,[210] the main statute, by virtue of which subsidiary legislation ('S.L.') has been adopted, that allows for the regulation, monitoring and enforcement of health and safety requirements at the workplace and the prevention of risks related thereto.

The CAD is transposed through S.L. 424.24 on the Protection of Workers from Risks Related to Chemical Agents at Work Regulations, dating back to 2003 and recently amended. The S.L. 424.24, article 7(1) refers to several other Regulations when it comes to arrangements to deal with accidents, incidents and emergencies, namely; "the first-aid, fire-fighting and evacuation measures as well as the warning and communication systems related to matters covered by these regulations including the Schedules hereto shall take place in accordance with the Work Place (First Aid) Regulations, the Work Place (Minimum Health and Safety Requirements) Regulations, and the Work Place (Provision of Health and, or Safety Signs) Regulations". The arrangements therein correspond to those of the CAD, as do the other provisions of S.L. 424.24.

The CMD is mainly transposed through S.L. 424.22 on the Protection of Workers from Risks Related to Exposure to Carcinogens or Mutagens at Work Regulations, also dating back to 2003 and recently amended. Reprotoxic substances are not regulated separately and are not included in the scope of the SL 424.22.

X3.6.20 Netherlands

The Netherlands has 3 acts which together form the Working Conditions Legal Instruments: The Working conditions Act of 18 march 1999 (AW), The Working Conditions Decree of 15 January 1997 regarding the safety, health and wellness in the workplace (AB), The Working Conditions Regulation of 12 March 1997 (AR) implementing provisions of the Working Conditions Decree.

First, the AW forms the basis of the occupational health and safety legislation in the Netherlands and contains the general provisions applicable to workplaces. Next, the AB is an elaboration of the AW and contains rules that both employer and employee must abide to prevent occupational risks. Last, the

[210] Chapter 424 of the Laws of Malta

AR is again, a further elaboration of the AB and includes more specific rules that are mandatory for employers and employees.

All three measures implement the provisions of the CAD, while the CMD is dealt with through the Law and Decree. Contrary to what is provided in the 2012 Milieu Report and the responses to the first consultations, we received confirmation that the provisions of the CMD have not been extended to cover reprotoxins. Although the Netherlands sets out additional requirements within its transposition of the CAD and the CMD, the measures broadly correspond to the implementation of both Directives.

X3.6.21 Poland

In Poland the CAD is implemented by Ordinance of the Minister of Labor and Social Policy on the maximum permissible concentrations and intensities of harmful health factors in the work environment of 23 June 2014. The CMD is implemented by Ordinance of the Minister of Health on chemical substances and their mixtures, agents or processes with carcinogenic or mutagenic in the workplace of 24 July 2012.

Poland has implemented both Directives without further obligations, with a few exceptions notably with regard to record keeping for information on CMR activities and sending information to the regional competent inspector.

Reprotoxins have neither been included in the scope of the CMD nor are they subject to particular legislation.

X3.6.22 Portugal

The requirements of the CAD and the CMD have been transposed through specific legislation, respectively, The Law 290/2001 of 16 November 2001 transposing into national law the CAD, and the Decree-Law 301/2000 of 18 November 2000 which regulated the protection of workers from risks related to the exposure to carcinogens or mutagens at work.

Portugal provides additional details with regard to certain requirements but has faithfully transposed the CAD and the CMD without extending the scope of the latter to include reprotoxins.

X3.6.23 Romania

The main act ruling the work relations and labor conditions is the Labour Code, enacted as Law no 53/2003, which establishes the general rules and the principles for occupational health and security. Its provisions are further developed by specific legislation.

The main regulation transposing the CMD is the Governmental Decision No.1093/2006[211] (GD 1093/2006) on Carcinogenic and mutagenic agents, enacted subsequently to the Labour Code approved by the Law No 53/2003.[212] Guidelines for a simplified procedure of risk assessment has been developed subsequent to GD 1093/2006 in co-operation with IRS France.

[211] Hotararea Guvernului nr. 1093/2006 privind privind stabilirea cerin elor minime de securitate si sanatate pentru protec ia lucratorilor impotriva riscurilor legate de expunerea la agen i cancerigeni sau mutageni la locul de munca, Publicata in Monitorul Oficial, Partea I nr. 757 din 06/09/2006

[212] Legea nr 53 din 24 ianuarie 2003 CODUL MUNCII, publicat în Monitorul Oficial nr. 72 din 5 februarie 2003, cu modificarile ulterioare; RPA, Milieu Report 2012, p.325.

Requirements for replacing carcinogens and mutagens are strengthened for some industrial area by environmental legislation transposing Directive 1999/13/EC, the operator being obliged to communicate to environmental authority the reduction scheme and phasing out of substances, if activities falls under provision of Solvent Directive.

The rest of the CMD requirements were accurately transposed just as those of the CAD which has been transposed by Governmental Decision 1218/2006[213] (GD 1218/2006).[214]

X3.6.24 Slovakia

The CAD is mainly transposed through the provisions of the Governmental Decree No 355/2006 on the protection of employees from the risks related to exposure to chemical factors at work. Decree sets out some precisions with regard to risk assessment and information of workers.[215]

The main provisions of CMD are transposed by the Governmental Decree No 356/2006 of 10 May 2006 on the protection of employees from the risks related to exposure to carcinogenic and mutagenic factors at work. Slovak legislation almost literally transposes the CMD provisions, meaning it does not refer to reprotoxic substances. It is more stringent and precise in excluding certain groups persons from work with carcinogens and mutagens, as well as the conditions under which such substances may be used in schools, universities and research workplaces. The legislation is also more stringent when it comes to access to risk areas, hygiene and individual protection.[216]

X3.6.25 Slovenia

The CAD has been transposed into the Slovenian legislation by the Rules on the Protection of Workers from the Risks Related to Exposure to Chemical Substances at Work of 11 December 2001 (Ur.l. RS No 100/2001).

The CMD has been transposed into Slovenian legislation with the Rules on the Protection of Workers From the Risks Related to Exposure to Carcinogenic and Mutagenic Substances of 13 October 2005 (Ur. l. RS No 101/2005). The transposition of the main text of the Directive is correct and almost literal, and reprotoxins are not included.

Both transpositions correspond to the measures set out in the CAD and CMD with no additional requirements except for the CAD requirement with regard to information and training of workers.

X3.6.26 Spain

The CAD is transposed by Royal Decree 374/2001 on the protection of health and safety of workers from risks related to chemical agents at work. The Decree sets out more detailed obligations when conducting risk assessments and dealing with accidents, incidents and emergencies.[217]

The transposing provisions of CMD are included in the Royal Decree 665/1997 on the protection of workers from risks related to exposure to carcinogens at work. The Spanish legislation has the same

[213] HOTĂRÂRE nr. 1218 din 6 septembrie 2006 privind stabilirea cerinţelor minime de securitate şi sănătate în muncă pentru asigurarea protecţiei lucrătorilor împotriva riscurilor legate de prezenţa agenţilor chimici, publicată în MONITORUL OFICIAL NR. 845 din 13 octombrie 2006

[214] RPA, Milieu Report 2012, pp.325-327.

[215] RPA, Milieu Report 2012, pp. 343-345.

[216] RPA, Milieu Report 2012, pp. 341-342.

[217] RPA, Milieu Report 2012, pp.354-362.

scope than CMD and does not cover reprotoxic. Most provisions were correctly transposed with on occasion, some variance in wording. The only additional requirements concern hygiene and individual protection as well as information and training for workers where more details are provided.

Annex 4 Threshold/Non-Threshold Paradigm

X4.1 Reprotoxic substances

Most of the studies on reprotoxins *in vivo* are focused on establishing a threshold or NOAEL. The EDC discussion, although far from over, raises the spectre of reprotoxins acting without (measurable) thresholds. In reality the situation probably is a hybrid: just like with carcinogens, some reprotoxins may not have a (measurable) threshold whereas others do. All of this makes managing these chemicals under CAD or CMD a messy proposition; some would be under CAD, while others would be under CMD: not quite tenable, especially not so if changes in scientific theory (a given) would impute thresholds for chemicals for which a threshold is currently not ascertainable and vice versa.

X4.1.1 What is a threshold?

There are many definitions of a threshold[218] for which the simplest is the mathematical threshold: the dose below which the response is zero, and above which it is nonzero. A simple definition and unfortunately unascertainable in standard biological and toxicological testing systems: uncertainty and the variability of biological responses does not allow for a true mathematical test.

The more precise definition is a biological threshold below which (adverse) effects from chemical exposure would not occur. In principle this is measurable and assumed to be (near) measurable in an Adverse Outcome Pathway (AOP). Unfortunately (nearly) all scientific measurements suffer from uncertainty which can only approach zero in an idealised experiment.

Instead everyone has to use experimental thresholds, the dose below which no (adverse) effect(s) is observed. This threshold is what we usually refer to in our threshold discussions, a concept that is associated with limitations of experimental design (and budget restrictions). This involves deriving a NOAEL/LOAEL or other experimental parameters of more limited use such as a LOAEL in the absence of a NOAEL (see the figure below).

Statistical significance does not address the question of adverse effects or biologically significant effects. The two are not identical[219]. Adverse effects affect the performance of organism to respond to an additional environmental challenge. Biologically significant effects on the other hand are responses that have substantial or noteworthy effect on the wellbeing of the biological system. This is in contrast to "statistically significant changes which may or may not be meaningful to the health of the biological system." Note that in practice all statistically significant changes are treated as adverse i.e. a NOAEL instead of a NOEL, mostly because our test systems only have a very limited number of measured parameters.

Statistical significance does not signify biological significance. However, experimental thresholds are the only way we can presently measure thresholds, although the advent of Adverse Outcome Pathways (AOPs) may refine our experimental thresholds.

[218] Slob et al 1999 Thresholds in toxicology and Risk Assessment Int. J. Toxicology 28, 259-268 as cited in JRC Scientific and Policy Reports, 2013: Thresholds for Endocrine Disruptors and Related Uncertainties http://publications.jrc.ec.europa.eu/repository/bitstream/JRC83204/lb-na-26-068-en-n.pdf

[219] Lewis, R.W. et al, 2002. Recognition of Adverse and Nonadverse effects in Toxicity Studies; Toxicologic Pathology 30(1) 66-74

X4.1.2 Adverse Outcome Pathways (AOPs)

AOPs are our current approach to molecular thinking behind and beyond our classical approach of x animals exposed, y animals affected. AOPs, based on molecular evidence, suggest a pathway through which a particular molecular interaction brings about an organ level response. Chemicals do not act on a liver directly: most often they affect an enzyme in such a way that when x concentration of chemical y is exceeded a gross effect on the organism can be observed. Note that we have just redefined a threshold: a concentration above which a biological cascade will lead to a gross/measurable effect. At the same time, while decreasing the uncertainty on the biological significance side, we have introduced a new uncertainty: the magnitude of the intracellular concentration necessary to initiate the response and how this correlates to gross exposure. In other words we are now more certain of where (if any) the threshold occurs on a (intra)cellular concentration level but we are very unclear on how this relates to the amount of exposure. Our understanding of toxicokinetics is mostly limited to correlation of doses to circulating levels of chemicals, not to the intracellular levels of chemicals.

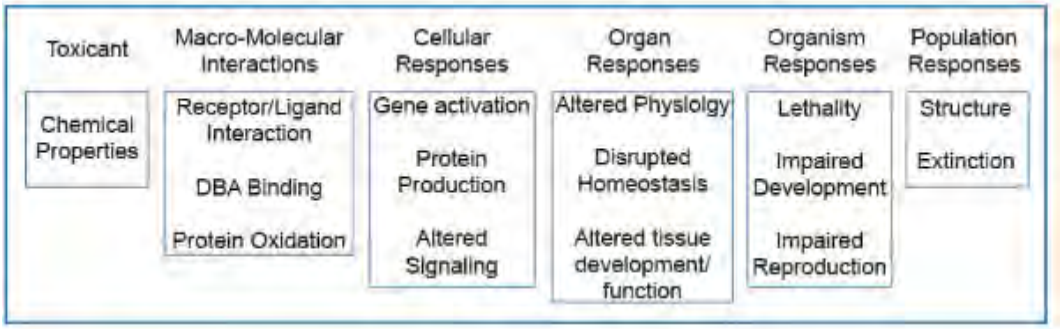


Figure X4-1: Schematic of an Adverse Outcome Pathway[220]

The above schematic describes the steps in an AOP along the top of the figure starting with Toxicant exposure, followed by what used to also be called the Molecular Initiating Event, now referred to as Macro-Molecular Interaction(s). Cellular responses, organ responses and organism responses follow. (Population responses are mostly related to ecotoxicological responses.) Note that this is a conceptual framework: details such as metabolism, enzyme binding, etc. all have to be filled in.

Having said all of this, a properly designed AOP can aid tremendously in our understanding of thresholds (where applicable) and the cascade of biochemical/biological effects brought about by intracellular exposure to a chemical. Although a lot of AOPs are still in the design phase, several AOPs related to reprotoxins have moved beyond that, and will most likely be tested against more traditional experimental methods.

For illustrative purposes we selected one example from the AOPWIKI[221], the public database where scientists maintain nearly all AOPs, most in the design phase (where they are not citeable.) Our selected sample is https://aopwiki.org/aops/30, "Estrogen receptor antagonism leading to reproductive dysfunction". This is an ecotoxicological example, but the cellular mechanism is thought to hold true across organisms (a discussion of this aspect is beyond the scope of this document.)

[220] Adapted from http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm Accessed 26 November 2018

[221] https://aopwiki.org/

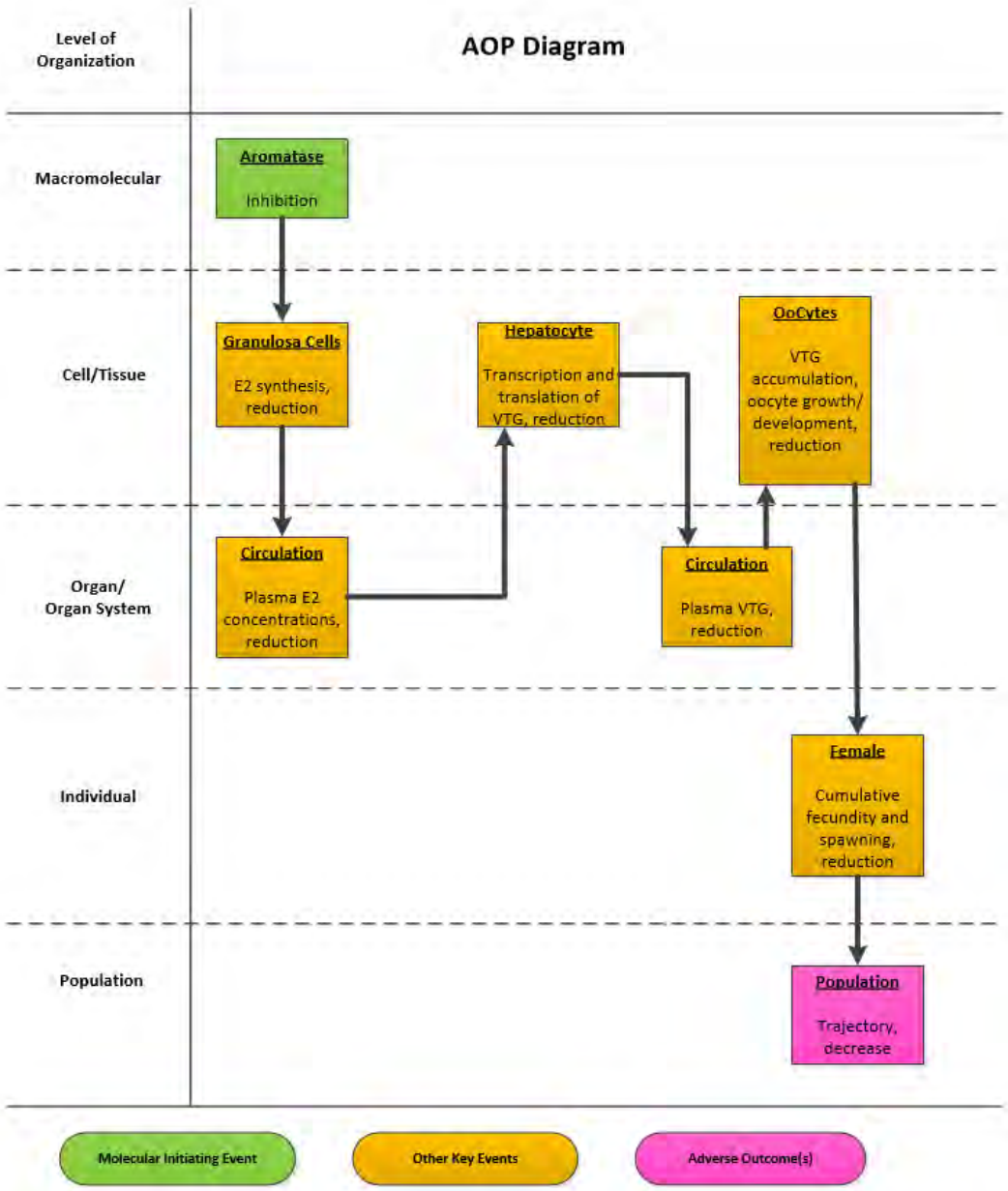


Figure X4-2: AOP for Aromatse Inhibition leading to decreased Fecundity[222]

The Molecular Initiating Event is thought to be aromatase (an enzyme) inhibition, unclear whether this would be direct action or via a metabolite. A cascade of cellular/organ level events leads to reduced oocytes. The reduced oocyte counts then lead to reduced female fecundity.

Where do thresholds come in? Obviously, the Molecular Initiating Event would be one threshold: at what concentration does aromatase inhibition begin. This is not the only threshold however.

[222] Adapted from https://aopwiki.org/aops/25

Homeostasis (the feedback process whereby organs/cells deal with perturbations) may be able to accommodate certain fluctuations[223] within aromatase inhibition: another threshold(s). Multiple AOPs may have to be joined to elucidate more detailed mechanisms and the AOP wiki is aimed at just that: collaborative efforts.

X4.1.3 Dose –Response curve and Threshold

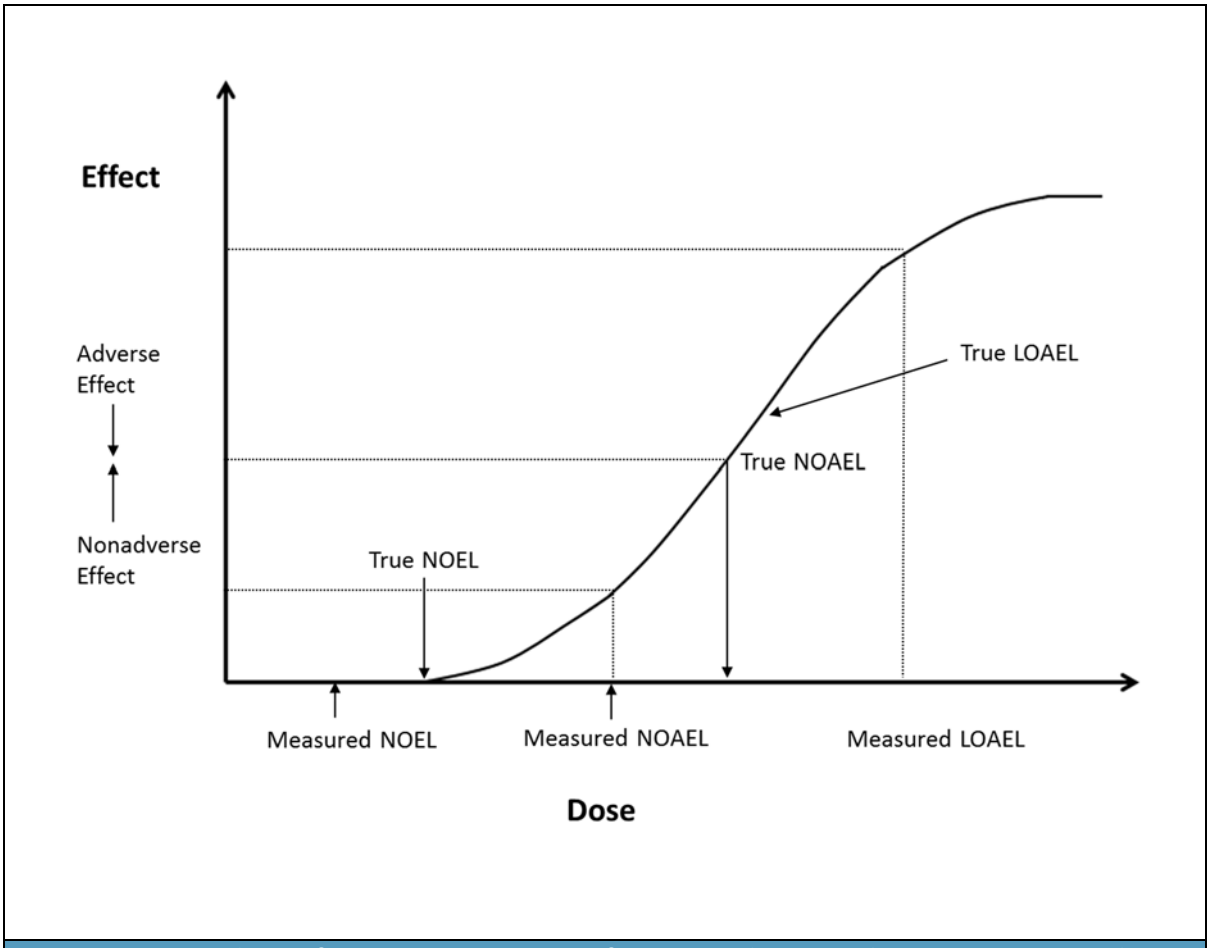


Figure X4-3: Dependency of qquantitative outcome of toxicity studies upon observation points. Redrawn from Lewis, R.W. et al, 2002. Recognition of Adverse and Nonadverse effects in Toxicity Studies; Toxicologic Pathology 30(1) 66-74

Thresholds are often derived in an imperfect way. As shown in Figure X4-3, there is nearly always a discrepancy between NOAEL, measured and actual (and for that matter LOAEL). It is interesting to note that measured NOAEL is always greater than measured and actual NOEL. LOAEL obviously starts right above NOAEL, and is thus often measured at a much higher level than actual[224]. Note that measured LOAEL is always higher than true LOAEL and the opposite is the case for NOAEL and NOEL. This dose-response curve is idealized: no accommodation has been made for statistics. Such studies often use very small number of animals – exposure groups of ten are common. Variability thus tends to be high and NOAEL measured data are often raised even further than indicated in the figure due to

[223] Almost certainly aromatase activity is not constant – this AOP does not for instance model aromatase induction.

[224] This is one of the reasons why conversion of measured LOAEL to a presumed NOAEL uses a much higher "safety factor" than appears to be justified at first glance, even more so for a NOEL.

"statistical significance", similarly for LOAELs. Most studies do not (clearly) distinguish between adverse and non-adverse effects[219,225].

X4.1.4 Thresholds of Toxicological Concern: TTC concept.

TTC is the process of setting thresholds without data, a concept mostly borrowed from cosmetics[226]. As contrarian as this may seem, it is a concept that has many followers because it *a priori* assumes there is a *de minimis* level of no concern (read threshold for adverse effect). TTC is primarily reserved for data-poor chemicals that do not belong to certain classes of high concern e.g. polychlorinated dibenzofurans. As soon as data becomes available, obviously TTC's need to be reviewed and where necessary, adjusted.

TTC for reprotoxins as a class have been "established". Such TTC's are derived by reviewing existing data-rich substances, deriving a NOAEL and applying a "safety factor" of 1000. Data ranged from 1 to 100 µg/kg body weight/day, the usual TTC unit. Such a TTC would thus be used to determine whether a concern for testing exists, i.e. an exposure dose of for instance 0.5 µg/kg bw/d would be considered below the *de minimis* value of 1, making further testing unnecessary under the TTC approach.

In this day and age of the desire and regulatory drivers for reduced animal testing, TTC is thus proposed for use in making a "test/ no test" decision. Review of ECHA dossier data using a TTC approach resulted in TTCs for rats and rabbits of 95-100 µg/kg bw for reproductive toxicity, using a safety factor of 100 in view of the larger database utilized. According to the authors any exposure below these TTCs may thus negate the need for testing. As noted such an approach has not yet received regulatory use nor approval. However, EFSA has long evinced interest in this approach and may be moving towards implementation of some form of TTC[227,228].

[225] An example would be decreased initial weight gain due to decreased palatability of the diet at higher concentrations of the chemical: a transitory effect, not an adverse effect.

[226] Hartung, T. 2017. Food for Thought.. Thresholds of Toxicological Concern – Setting a Threshold for Testing Below Which There is Little Concern ALTEX 34(3) 331- 351.

[227] EFSA, 2015. Thresholds of Toxicological Concern Approach: Conclusion and Recommendations of the EFSA/WHO Expert Workshop http://www.who.int/foodsafety/areas_work/chemical-risks/ttc20150212.pdf

[228] https://www.efsa.europa.eu/en/topics/topic/threshold-toxicological-concern, accessed 23 November 2018

X4.1.5 Non-Monotonic Dose Response

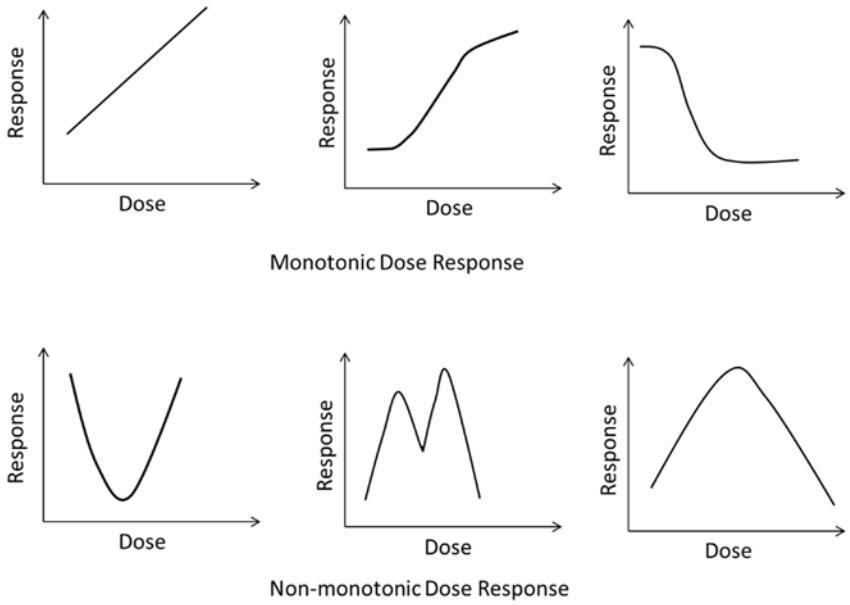


Figure X4-4: Examples of Monotonic vs Non-Monotonic doseresponse curves

Discussion of thresholds has so far assumed that the dose-response is monotonic i.e. with increasing dose one gets a continuous response whether it be negative or positive as shown in the first three graphs in Figure X4-4. This is the classic single key event with single effect outcome. This is often artificial because an exposure may give two completely different effects i.e. absolute decrease in body weight (gain) and an increase in hepatic enzyme levels. Even though they may have a common (molecular or biological) basis, such effects are often plotted on separate graphs and hence appear monotonic.

Imagine the result of two pathways affecting the same system – again hepatic enzyme levels. This time in a test tube we will see a two-hump dose response curve: one can imagine here two different pathways at work expressed on the same enzyme level. At first one sees direct effects from enzyme binding: Chemical A binds to receptor but receptor on enzyme can only accepts so much A, at which point the action of metabolite B on the same enzyme comes into action but metabolite B is only produced from the non-bound fraction of A – voila non-monotonic response. Two mechanisms of action expressed through a common indicator and here we have two monotonic dose response curves superimposed[229].

There still is a threshold, actually two: first from the first direct binding action and secondly from the metabolite action. One then still has to ensure that the effect above either of these thresholds is adverse. Most of such non-monotonic dose-response relationships will be more easily distinguished in *in vitro* test where numerous, i.e. >6, dose levels are easily accomplished whereas very few animal

[229] Not all non-monotonic dose-response curves are so easily resolved of course.

studies go to that level. Non-monotonic dose responses have been observed in *in vivo* studies[230] but not at high frequencies and surprisingly enough not just for reproductive effects.[231]

Many hormone-like EDC have been reported to have non-monotonic dose –response curves. Surprisingly enough these results are not consistent. For Bisphenol A for instance, only 20-30 % of studies showed non-monotonicity where the frequency increased with the number of doses used in the *in vitro* experiments[232]. It was unclear whether the role of cytotoxicity in non-monotonic responses was evaluated. There thus appears to be some evidence that *in vitro* non-monotonicity can occur. Until the definitive *in vitro* vs *in vivo* study (BPA CLARITY) has been performed, it will be unclear how the *in vitro* data can be extrapolated to *in vivo* data for risk assessment purposes.

[230] EFSA 2016. Review of non-monotonic dose –responses of substances for human risk assessment. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2016.EN-1027

[231] Unclear as to whether all or any of these effects are thought to be mediated by hormonal activities.

[232] Vandenberg, L. 2014. Non-Monotonic Dose Response in Studies of Endocrine Disrupting Chemicals: Bisphenol A as a Case Study. Dose-Response 12; 259-276 https://journals.sagepub.com/doi/pdf/10.2203/dose-response.13-020.Vandenberg

Annex 5 Sensitisers

In this annex, other types of chemicals, which are not primarily reprotoxic chemicals and currently within the scope of the CAD will be discussed. A question still remains whether a threshold-type mode-of-action should be assumed for risk assessment/management purposes (for sensitisers) and whether it would be useful to include these chemicals within the scope of the CMD, especially in the absence of a.

X5.1 Preliminary remarks

Much has been written in recent times regarding the topic of sensitisers and especially the (in)ability to derive thresholds especially for respiratory sensitisers. Diverging opinions exist as to whether this is possible or whether they even exist. If no thresholds can be identified and this is a problem for all sensitisers as a group then this may indicate that sensitisers should be regulated under CMD. If however this is not the case than CAD might be the appropriate regulatory vehicle. As is often the case in science, opinions are divided: the (semi)consensus appears to be that theoretically sensitisers should have thresholds. In practicality however some of these thresholds may be hard to derive because they are very small or with so much variability that selecting a single numerical threshold may simply not be possible at this time. Improvements in science especially the measurements of MIE's in appropriate AOPs (see below) may provide a mechanistic pathway by which to quantify a threshold, eventually. In short what we have here is a transitional science where neither CMD nor CAD provides a fully comprehensive regulatory directive, although one or the other could eventually prevail for most of the sensitisers. Therein lies the problem: neither approach (CMD/CAD) provides a fully satisfactory approach: some hybrid approach is obviously required.

Regulators and regulees seem to be in agreement that improvements in the management of sensitizers are needed. Some regulators (Finland) and others (industry/union pr) agree that the CAD and CMD no longer have the scientific backing they once had, i.e. the threshold concept that once separated them, no longer holds true. Carcinogens have (practical) thresholds, sensitisers may have negligible thresholds (for now): the (old) distinction no longer holds. Exposure controls whether barrier PPE (gloves and aprons in the case of skin sensitisers) as well as process improvement may do much to reduce exposure[233]. Cessation or reduction of exposure can reverse some symptoms, also differing from the effects of CM substances under the CMD. Thresholds or lack thereof is thus not the only distinguishing aspect between CMD and CAD.

Skin and respiratory sensitisers can also be designated as substances of very high concern (SVHC) according to the criteria laid down in Article 57 (f) of the REACH Regulation. SVHC on the REACH Candidate list are candidates for being included in REACH Annex XIV, leading to the requirement of authorisation for further use.

ECHA presented a discussion paper [234] assessing properties of skin and respiratory sensitisers as compared to properties of CMR substances. The question was raised as to whether derivation of a 'safe concentration' is possible? Only for reproductive toxicants was the outcome affirmative, while for carcinogen, mutagenic, respiratory and skin sensitisers it was deemed not possible. As this appears

[233] http://www.cefic.org/Documents/IndustrySupport/REACH-Implementation/Guidance-and-Tools/Cefic-Position-on-Skin-Sensitisation.pdf

[234] https://echa.europa.eu/documents/10162/13657/svhc_art_57f_sensitisers_en.pdf , accessed 1 October 2018

to date to 2012 the advice and conclusions re non-thresholds for carcinogens especially, seems to have been overtaken by newer science.

In Annex A.3 "Dose-response relationship" of ECHA's discussion paper[234] it is further explained that although the existence of dose-response relationships for both skin and respiratory sensitisers is acknowledged, it might be difficult to establish threshold doses for both the induction and the elicitation phase (see below for further explanations), due to the interdependency of both, inter-individual differences in responses and the lack of validated experimental models.

X5.2 Mechanism of sensitization

The major problem with sensitisers thus lies in the underlying biological mechanism. Although thresholds should exist, our understanding of the mechanism as further detailed in the AOP section below is still evolving and until we have a full understanding, we will be unable to make a quantitative determination of potency and hence threshold, especially in view of the poor sensitivity and specificity of our current animal models.

There are two major phases: *Initiation* - first contact, leading to the primary immune reaction (in general without symptoms) and *Elicitation*: contact after initiation, leading to allergic symptoms.

Our present understanding is that the process of sensitization goes through the following cascade:

- Formation of hapten-protein conjugates, by electrophilic reaction;
- Cellular danger signalling (expression of inflammatory cytokines and chemokines and activation of cytoprotective gene pathways);
- Recognition, uptake and processing of antigen by dendritic cells;
- Migration of activated dendritic cells and presentation of antigen to responsive T-lymphocytes;
- Activation and clonal expansion of T-cells.

All of the above processes follow typical biological dose-response relationships, in principle allowing for the determination of thresholds.

X5.3 AOP: Adverse Outcome Pathway

An "Adverse Outcome Pathway" was established for skin sensitisation by OECD, which reflects the current mechanistic understanding of skin sensitization (OECD, 2012a; b, graphic in [235]). The following key events were identified, where the Molecular Initiating Event or MIE appears to follow standard dose-response equations:

- Exposure/ dermal absorption of the chemical;
- Molecular Initiating Event: interaction of the chemical with skin proteins (covalent bindings to cysteine and/or lysine residues);
- Induction of inflammatory responses in keratinocytes/ Langerhans cells as well as gene expression associated with particular cell signalling pathways (e.g. antioxidant/electrophile response element-dependent pathways);

[235] Cohen, J.M., et al, 2018. Expanding the toolbox: Hazard-screening methods and tools for Identifying Safer chemicals in green product design. ACS Sustainable Chemistry & Engineering, 6, 1941-1950; DOI; 10.1021/ACSSUSCHEMENG.7B03368

- Activation of dendritic cells (typically assessed by expression of specific cell surface markers, chemokines and cytokines);
- T-cell proliferation;
- Organ Response (antigen presentation in lymph node; and
- Organism response.

X5.4 In silico models and prediction

Many in silico models for prediction of (skin) sensitization exist. In general, respiratory sensitizers also test positive in skin sensitization tests, not surprising given that the consensus is that respiratory sensitization can be initiated via skin exposure. The predictive capability of all animal, in vitro and in silico methods by themselves is lousy. Specificity[236] barely passes 50% and only for some models. Only a combination of various methods leads to accuracy exceeding 90%, sufficient for identification purposes. Unfortunately none of the tests reliably (yet) provide AOP/MIE data useful for assessing the potency of the sensitiser.

Human Data Prediction using all available Data [237]		
Model	Sensitivity	Specificity
Human	0.94	0.70
LLNA	0.65	0.54
DPRA	0.84	0.50
KeratinoSens	0.84	0.24
h-CLAT	0.92	0.22
Bayesian Model	0.94	0.84

X5.5 Respiratory sensitisers

Respiratory sensitisation is a well-known phenomenon, leading to severe consequences including life-threatening conditions (Arts et al., 2006). It can be induced by natural and man-made materials and substances. Examples for natural materials are proteins from moulds or mites[238]. Respiratory allergy caused by chemicals is defined as an immune-mediated hypersensitivity reaction to an exogenous low molecular weight chemical. The symptoms of such a reaction are asthma and rhinitis (Cochrane et al., 2015).

The following observations can be important from a regulatory point of view:

- Effect levels for both stages (induction and elicitation) vary from substance to substance and concentrations leading to elicitation are often, but not always lower than those for initiation (Arts et al., 2006).
- High peak exposures seem to be an effective way for induction (Arts et al., 2006).
- Growing evidence shows that respiratory sensitisation cannot only be induced by inhalation exposure, but also by skin contact (Cochrane et al., 2015).

[236] Sensitivity: ability to detect those with the disease or true positive rate. Specificity: ability to correctly identify those without the disease or true negative rate.

[237] Alves, V.M., et al, 2018. A perspective and a new integrated computational stragey for skin sensitization assessment. ACS Sustainable Chemistry & Engineering, 6, 2845-2859.

[238] https://osha.europa.eu/en/tools-and-publications/publications/factsheets/39

- Respiratory sensitisers prove positive in the Local Lymph Node Assay (LLNA) for skin.sensitisation (Basketter et al., 2017; Chary et al., 2018).

Nevertheless, OELs set in the past for respiratory sensitisers were successful in significantly reducing the observed cases, similar to OELs for substances with other toxicological endpoints.

Summarising the discussion, it can be concluded that although there is no biological reason to assume that thresholds do not exist for respiratory sensitisation, routine determination of safe levels has proven difficult due to the individual variability, (inter)dependency of induction and elicitation phase and the lack of validated experimental models.

X5.6 Skin sensitising substances

Skin sensitisation is an immune-mediated cascade of events, which occurs via two distinct phases, induction and elicitation. The most obvious difference is that both phases are triggered by dermal contact with the sensitiser.

The principle of the existence of thresholds for skin sensitisation is acknowledged by the experts in the field since many years (Boukhman and Maibach, 2001; Kimber et al., 1999). But it is also recognized that such doses depend on conditions such as size of skin area the substance is applied to, the anatomical site, number of exposures, the vehicle and occlusive/non-occlusive conditions (Basketter et al., 2002; Boukhman and Maibach, 2001).

There is a broad historical human database on skin sensitisation with many substances investigated in the Human Repeated Insult Patch Test (HRIPT) and/or the Human Maximisation Test (HMT) (Basketter et al., 1997; Boukhman and Maibach, 2001). Exposure levels not leading to sensitisation induction under the conditions of these tests were established. Also for the elicitation phase, dose-response relationships and thresholds were identified, below which allergic symptoms are unlikely to occur (Ezendam et al., 2012; Fischer et al., 2016; Jerschow et al., 2001). Please note that even the human tests are not highly specific (see table above.)

In summary, risk assessment frameworks have been proposed to derive acceptable exposure levels (expressed as mg substance per skin area). The principal applicability of threshold concepts is not disputed in the literature. But their practical relevance is in areas where the dose per skin area can be reasonably estimated, e.g. in the area of cosmetics safety.

X5.7 Thresholds

The consensus of the competent experts and authorities seems to be that thresholds for induction do exist:

Skin sensitisers:	thresholds for adverse effects (induction of sensitisation) exist and health-based reference values based on the threshold assumption can likely be determined (despite some methodological difficulties)
Respiratory sensitisers:	thresholds for adverse effects (induction of sensitisation) exist, but – with currently available models and methods - are difficult to determine

However as noted, the experimental methods in use including in silico models are not advanced enough to determine accurate thresholds (for use in standard setting) at this time especially in view of the highly variable sensitive populations that exist within the workforce. PPE on the other hand has proven very effective in preventing especially skin sensitization.

A dissenting view was expressed by a government stakeholder that commented on this conclusion: problems with respiratory sensitation can be very individual and classification might be based on case studies not significant for the majority of workers and working conditions. Also, for respiratory sensitisers there must be "practical thresholds" simply based on the observation that - with 300-400 sensitisers - the number of occupational respiratory sensitization is limited.

X5.8 Risk management considerations

With the setting of mode-of-action based thresholds and derivation of OELs by RAC for substances such as benzene (RAC, 2018) the strict dividing line between threshold substances and non-threshold substances is blurring.

Quantifying skin exposure to sensitisers is not exactly an exact science, so human dose –response relationships would be difficult to establish. For respiratory sensitisers derivation of a health-based OEL will most likely depend on the amount of quantitative human data from workplace experience and it might be possible or not on a case-by-case basis.

Annex 6 Health Effects Considered for Bottom Up Analysis

Table X6-1: Summary of effects identified from published literature		
Substance	**Monetisable effect**	**Effects identified from literature**
Lead **Lead di(acetate)** **Trilead dioxide phosphonate**	Spontaneous abortion or still birth	Increased Odds ratio for spontaneous abortion Increased incidence of stillbirth *Increased pup mortality (dead pups number)* *Increased incidence of reduced number of litters up to PND 23*
	Low birth weight	Increased frequency of preterm births Decreased birth weight Decreased crown-to-rump length (CRL) -female Reduced foetus weight at birth Decreased birth weight of foetus-male Decreased birth weight of foetus-female *Decreased pup body weight at age 5 day*
	Impaired fertility - male	Reduction in fertility Reduction in median sperm concentration Decreased sperm count Decreased Gross Sperm motility Increased sperm liquefaction time Lower sperm counts Decreased sperm concentration Decreased total sperm count
	Impaired fertility - female	Reduced circulating concentration of progesterone *Reduced number of foetuses / dam* Reduced number of implantation sites/dam Increased incidence of disrupted oestrous cycle (F1)
	Reduced foetal growth	Decreased crown-to-rump length (CRL) -male
	Impaired cognitive development – IQ	Inverse associations between the maternal blood lead levels and the Neonatal behavioural neurological assessment scores
	Developmental neuro-impairment	
	No monetisable effect correlate	Delay in puberty with increased age at menarche Reduction in 6-month head circumference at delivery Decreased anogenital distance (AGD)-male Decreased anogenital distance (AGD)-female Decreased AGD/CRL ratio-male Decreased AGD/CRL ratio-female Increased incidence of delayed vaginal opening (F1) Reduced foetus weight on postnatal day 23-male Reduced foetus weight on postnatal day 23-female Decreased offspring body weight at weaning-male Decreased offspring body weight at weaning-female Decreased offspring body weight at puberty-male Decreased offspring body weight at puberty-female Decreased offspring body weight at post puberty-male Decreased offspring body weight at post puberty-female

Table X6-1: Summary of effects identified from published literature		
Substance	**Monetisable effect**	**Effects identified from literature**
Bisphenol A (BPA)	Spontaneous abortion/still-birth	*Decrease in # of live pups/litter* *Decrease in # of live pups*
	Impaired fertility – female & male	*Decrease in mean # pups* *Decrease in mean # litters/pair*
	Impaired fertility – offspring*	Decreased seminal vesicle weight in F1 males Reduced epididymal sperm concentration (F1) Reduced daily sperm production/testis (F3)
	Impaired fertility - female	Epithelial hyperplasia (Vagina) Dilatation of lumen in uterus
	Impaired fertility – female & offspring*	Increased gestational length (F0 and F1)
	Impaired fertility – male	Decreased epididymal sperm concentration (F0)
	Reduced foetal growth/low birth rate	*Increase in cumulative days to litter*
	No monetisable effect correlate	Increased paired ovarian primordial follicle count (F0) *Decreased mean pup body weight/litter-PND-21-male (F1)* *Decreased mean pup body weight/litter-PND-21-female (F1)*
Borates	Impaired male fertility	Decrease in mating Index Decrease in fertility Index Decrease in right testis weight (F0) Decrease in right caput and corpus epididymis Decrease in prostrate weight (F0) Decrease in right cauda epididymis weight in F0 males
	Reduced foetal growth	Decrease in offspring body weight/litter-male (GD20) Decrease in offspring body weight/litter-female (GD20) Decrease in foetal body weight/litter Decrease in foetal body weight *Decrease in adjusted live pup weight*
	Developmental abnormality	*Increase in offspring with short rib XIII/litter (GD20)* *Increased % malformed foetuses/litter (skeletal malformation)*
Imidazolidine-2-thione (ETU)	Impaired cognitive development	Decrease in Iodine uptake
	Spontaneous abortion or still birth	*Increase in Resorption sites and dead foetuses (mean/litter)* Decreased mean no. of live foetuses Increase in % foetal death Decrease in mean no. of foetuses Increased incidence of foetal death
	Reduced foetal growth	*Decrease in male foetal body weight per litter* *Decrease in female foetal body weight per litter* Decrease in mean foetal weight Decrease in foetal body weights-male Decrease in foetal body weights-female Decrease in foetal weight

Table X6-1: Summary of effects identified from published literature		
Substance	**Monetisable effect**	**Effects identified from literature**
		Decrease in foetal Crown-Rump length
	Spina bifida	Increased incidence of dumbbell-shaped or blobbed vertebral centra Increased incidence of cranial meningocele Increased incidence of cranial meningorrhea
	Skeletal effects or abnormalities of the limbs	Increased incidence of severe hind limb talipes *Increased incidence of short and/or kinky tail* *Increased incidence of short or kinky tail* *Increased incidence of tail anomalies*
	Developmental neuro-impairment	Increased incidence of dilated brain ventricles
	Renal abnormalities	Increased incidence of hydro ureter Increased incidence of dilated ureter
	Foetal anomaly	*Increase in % total malformed foetuses*
	ADHD	Increase in total activity score (F1)
4-tert-butylbenzoic acid (pTBBA)	Impaired male fertility	Reduction in relative testes weights Reduction in mean relative testes weight Lower testicular sperm counts Reduction in mean sperm count Infertility/inability to impregnate
2-Ethoxyethanol (EGEE)	Impaired fertility – male	Decreased sperm motility Increased abnormal sperm Decreased fertility index Decreased relative right testes weight Decrease in sperm concentration Increase in oestrous cycle length in females Decrease in relative epididymis weight Decrease in spermatid count Decrease in spermatid head count Motility and progressiveness of sperm
	Impaired fertility – female	Increased pre-implantation loss *Decreased litters per fertile pair* *Decreased live pups per litter* *Increased resorptions per litter* *Increased mean resorptions per litter*
	Impaired fertility – male Impaired fertility – female	*Decreased number of live foetuses* *Decreased live foetuses per litter*
	Spontaneous abortion/still-birth	*Decreased proportion of pups born alive*
	Renal abnormalities - offspring	Increased renal pelvic dilation Renal changes (minor anomalies) Renal malformation
	Cardiovascular abnormalities	Increased cardiovascular defects Cardiovascular malformation
	Skeletal abnormalities of the limbs	Increased no. of foetuses with limb malrotation

Table X6-1: Summary of effects identified from published literature		
Substance	**Monetisable effect**	**Effects identified from literature**
	No monetisable effect correlate	*Decreased Live pup weight* Increased % of foetuses with minor external and visceral defects Increased % of foetuses with minor skeletal defects Increased skeletal minor defects Ventral wall defects (major malformation) Fused aorta and pulmonary artery (major malformation) Increased foetuses with extra ribs *Increased foetuses with vertebral variations* *Increased foetuses with sternebral variations* Rib dysmorphology *Supernumerary ribs per litter* *Increased incidences of reduced ossification per litter* Brain malformation
2-Ethoxyethanol acetate (EGEEA)	Impaired fertility – female	Increased post-implantation loss
	Impaired fertility – male Impaired fertility – female	Decreased mean no. of live foetuses
	Skeletal abnormalities of the limbs	Increase in the rates of any skeletal defects
	Cardiovascular abnormalities	Cardiovascular malformations
	No monetisable effect correlate	*Decreased mean total litter weight* Increase in the rates of external and visceral minor defects Decrease in foetal weight
2-(4-tert-butylbenzyl)propinolaldehyde (2,4-TBP)	Impaired fertility - male	Reduction in mean fraction of motile sperm in the cauda epididymis Increase in mean fraction of abnormal sperm Reduction in mean sperm head count in the cauda epididymis Testicular atrophy
	Impaired fertility - male Impaired fertility - female	Reduction in mean implantation sites Decreased litter size
	Spontaneous abortion or still birth	*Increased number of stillborn pups* *Decreased number of live born pups* Decrease in viability index
	Impaired fertility offspring – female (but can only value males)	Decrease in mean number of implantation sites (P1)
Phenol, dodecyl-, branched	Impaired fertility – female	Increased incidence of ovaries with decreased presence of corpora lutea (5 or less) (F0) Increased oestrous cycle length (F0) Decreased number of implantation sites (F0)
	Impaired fertility – female	Fertility index decreased Copulation index decreased

Table X6-1: Summary of effects identified from published literature		
Substance	**Monetisable effect**	**Effects identified from literature**
	Impaired fertility – male	
	Impaired fertility – offspring*	Increased incidence of ovaries with decreased presence of corpora lutea (5 or less) (F1) Decreased vaginal patency (F1 females) Increased oestrous cycle length (F1) *Decreased number of pups born (F2a)* *Decreased live litter size (F2a)*
	Impaired fertility – male	Decreased epididymis sperm concentration(F0)
	No monetisable effect correlate	Decrease in the ages of the first occurrence of oestrus *Decreased pup body weight-male-PND 7 (F1)* *Decreased pup body weight-female-PND 7 (F1)* *Decreased pup body weight-female-PND 21 (F1)* Increased incidence of skeletal malformations involving a curved scapula and/or abnormally shaped long bones
Phenol, dodecyl-, sulfurized, calcium salts	Spontaneous abortion/still-birth	*Increased number of dead pups at on lactation day 0 (F1 pups)*
Phenol, dodecyl-, sulfurized, carbonate, calcium salts, overbased	Impaired fertility – female	Pre-implantation loss
Organotins - dibutyltin dilaurate	Embryonic/ foetal development	Increased mandible complications Anomaly of mandibular fixation, cranial hypoplasia, and fused ribs
Organotins - dibutyltin dichloride	Fertilisation/ implantation	Higher number of non-pregnant females Higher pre-implantation loss *Increased number of litters totally resorbed* *Increased number of resorptions and dead foetuses per litter in early stage* *Increased post-implantation loss per litter* *Higher incidence of post-implantation loss per litter* *Higher incidence of post-implantation loss per litter* Increased post-implantation loss *Decreased number of live foetuses per litter* *Increased Pup mortality (F1)* *Higher number of resorptions and dead foetuses per litter* *Increased incidence of totally resorbed litters* *Increased incidence of litters totally resorbed* Decreased survival rate of foetuses at terminal caesarean sectioning *Decreased number of females with live-born pups* *Decreased number of pups delivered* *Decreased number of live-born pups* *Lower number of live foetuses per litter* *Lower number of live foetuses per litter* Decreased placental weight *Pup weight decreased on PN 4 (F1)* Decreased Gestation index *Pup weight decreased on PN 1 (F1)*

Table X6-1: Summary of effects identified from published literature		
Substance	**Monetisable effect**	**Effects identified from literature**
	Embryonic/ foetal development	Increased incidence of ovarian cysts in high-dose females Decreased body weights of live fetuses High incidence of foetuses with malformations (Cleft jaw and ankyloglossia were the most frequent malformations) Increase in the incidence of foetuses with skeletal malformations Increased incidence of foetuses with skeletal anomalies Increase in the incidence of foetuses with skeletal malformations Increased incidence of fused ribs and deformed vertebral column Increase in the incidence of foetuses with external malformations Increase in the incidence of foetuses with external malformation Higher incidence of foetuses with internal malformations Increased incidence of foetuses with internal malformations Increased mandible complications Increased incidences of foetuses with defect of the mandible and fusion of the sternebrae Increased incidences of foetuses with deformity of the vertebral column in the cervical and thoracic regions Increased fused ribs
Organotins – dibutyltin oxide & dibutyltin diacetate & dibutyltin maleate	Embryonic/ foetal development	Increased mandible complications Anomaly of mandibular fixation, cranial hypoplasia, and fused ribs
Organotins - Butyl(3-hydroxybutyl)tin dilaurate (3-OHDBTL)	Embryonic/ foetal development	Increased mandible complications Fused mandibula or micromandibula
Retinol	Skeletal effects or abnormalities of the limbs	Increased malformations: significant differences in foot length, biparietal diameter, occipitofrontal diameter and head circumference
	Low birth weight- includes hydrocephalus, bulging fontanelles and other congenital effects	Episode of bulging of the fontanelle
Dinoseb	Embryonic/foetal development	Foetuses with microphthalmia *Increased litters with external, internal and skeletal defects (mostly brain and spinal cord)* Decrease in foetal crown-rump length Decrease in foetal weight Reduced foetal birth weight per litter Reduced body weight on postpartum day 1 Reduced body weight on postpartum day 7

Table X6-1: Summary of effects identified from published literature		
Substance	**Monetisable effect**	**Effects identified from literature**
	Impaired fertility – male	Decrease in epididymal sperm count
	Impaired fertility – female	Decreased fertility index for 0-14 days post-treatment mating period Decreased fertility index for 104-112 days post-treatment mating period
	Spontaneous abortion or still birth	*Decreased litters with live foetuses* *Decrease in % of embryo survival rate per litter at Day 12* *Decrease in percentage of foetal survival rate per litter at birth*
Aprotic solvents	Spontaneous abortion or still birth	Parturition index *Live male foetuses/ litter* *Early resorption/ litter* *Live foetuses/litter* Number of dead implants *% resorptions per dam* % dead implants *Viable foetuses/litter* *Resorption sites/litter* Live birth index Viability Index
	Reduced foetal growth	Reduced body weight (21 days) Significant foetotoxicity (reduced bw) Foetal weight Mean foetal body weight 24 H viability index Lactation Index *Pup Body weight gain* *Offspring weight per litter* *Reduced pup body weights*
	Skeletal effects or abnormalities of the limbs	Foetal Malformations Soft tissue variations (% foetuses) Skeletal variations (% foetuses) Skeletal malformations Total malformations Extra 13th Rib
	Impaired fertility – female	Fertility/fecundity female parent
	Developmental abnormality	Abnormal appearance high dose Fetal Malformations Visceral Malformations Visceral Variations
Notes: *All fertility effects on the offspring are monetised as 'impaired fertility – male offspring' regardless of the gender of the affected individual. Effects in italics are animal effects only Source: Annexes 10-21 to this report.		

Annex 7 Strategic Approaches and Risk Management Measures

X7.1 Introduction

This Annex describes the types of risk management measures (RMMs) that are currently in place to comply with the CAD and CMD so as to minimise exposures to Repro. 1A and 1B chemicals. This includes:

- An overview of the RMMs in place for the set of 30 reprotoxins prioritised and consideration to the extent to which these measures are likely to be representative based on consultation responses and the literature.

- Examples of good/best practice in eliminating and/or managing occupational risks to reproductive health by following the hierarchy of preventive and protection measures under the CAD and CMD, again focused using the consultation responses.

The level of information gathered on these two aspects is limited by the quality of some of the responses to the targeted consultation as well as the number of responses. What we have found is that eSDSs often go beyond the REACH dossiers in what is "required" as RMMs. Some employers go even beyond the eSDS including initiating substitution of Reprotoxic 1A/1B substances thereby implementing (CAD and) CMD like requirements.

RMMs identified here are also taken into account in the case study work and when estimating the burden of disease arising from current exposures to the selected reprotoxins.

X7.2 Current Risk Management Measures

X7.2.1 Context

In undertaking these two Sub-tasks, we took as our starting point for identifying RMMs the REACH Registration dossiers, which provide the DNEL and/or OELs that act as the basis for assessing the risks from exposure and establishing the safe use of a Repro. 1A and 1B substances. RRMs are aids to achieving an DNEL in a hierarchical manner.

Chemicals classified as Repro. 1A and 1B, whether subject to harmonized classification or not, had to be registered under REACH by the first registration deadline (May 2010). If volume exceeded 10 tonnes, these registrations had to include a chemical safety report (CSRs) containing a risk assessment and proposed RMMs to manage and minimize the risks from identified uses. These CSRs should include exposure scenarios setting out the operating conditions and risk management measures needed to ensure that exposures occur at levels below the DNEL derived by the chemicals safety assessment. These measures are then communicated to downstream users through extended safety data sheets (eSDS)[239].

Employers should follow the conditions of use set out in the extended safety data sheets, unless their situation is different from that described in the e-SDS. In such situations, REACH places a duty on downstream users to carry out their own risk/safety assessment and to identify appropriate risk

[239] eSDSs are still not publicly available for all industrial chemical as became clear during a search for the SDSs for the aprotic solvenst added to the scope in September 2018.

management measures to ensure safe use. This aspect of REACH essentially reflects an overlap with the requirements that apply under the CAD.

CAD (Article 4.1) requires an employer to first determine whether any "hazardous chemical agents" are present in the workplace. If present, it requires the employer to undertake a risk assessment of exposures to workers arising from the presence of such a hazardous chemical agent. If the risk assessment reveals a risk[240], the employer must take specific protection, prevention and monitoring measures. CAD refers to (1) "general" and (2) "specific" protection and preventive measures (i.e. risk management measures):

1. General measures include the elimination or minimization of risks to the health and safety of workers by the design and organisation of systems of work, the provision of suitable equipment and maintenance procedures, the reduction to a minimum the number of workers exposed or likely to be exposed, etc. (Article 5);
2. Specific protection and prevention measures refer to the "substitution" by a not or less hazardous chemical agent, the measurement of chemical agents in relation to the occupational exposure limit on a regular basis, etc... (Article 6); and
3. Other RMMs are considered such as the establishment of effective procedures (action plans) for accidents, incidents and emergencies (Article 7) and information and training of workers (Article 8).

Similar requirements apply under the CMD. Article 4 requires the replacement (substitution) of C and M substances (at present), in so far as it is technically possible, by a substance that is not dangerous or less dangerous to workers' health and safety. When replacement (substitution) is not possible, then other risk management measures must be applied in a given "hierarchy", i.e. first use "in a closed system", and if not feasible, reduction of "level of exposure". A series of specific measures must also be taken under Article 5.5 with the aim of preventing and reducing exposures. Together these provide the basis for the so-called the so-called "STOP principle".

The STOP Principle states control measures needed to be implemented according to a strict hierarchy, with PPE as a measure of last resort:

[240] Where the risk is "slight" (undefined in CAD), the measures set out in Art. 6, 7 and 10 will not be applied to the extent that the preventive/general measures set out in Art 5(1) and 5(2) are sufficient to reduce the risk.

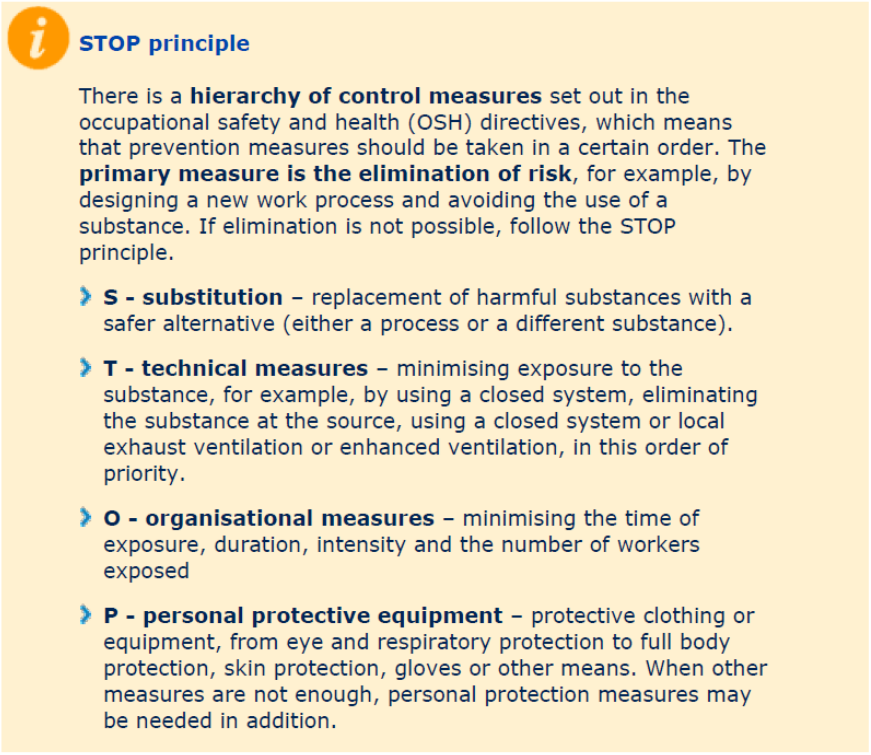


Figure X7-1: STOP principle241

In the targeted consultation, many non-industry representatives noted in response to that the exposure scenarios and RMMs described in eSDSs are often too general in nature to assist an employer in adopting effective RMMs. For example, general assumptions are made as to the efficiency of recommended RMMs, with no guidance given on how to measure this or on when the assumed efficiencies would not be realised. In many other cases, the recommended RMMs are not the same as the measures that are already in place in a given workplace. The existing measures were implemented in order to ensure that risks to workers are addressed, with this leading to some confusion for the employer. Often this results in duplication of effort and/or delayed implementation of RMMs.

The remainder of this sub-section describes the risk management measures (RMM) recommended under REACH (mostly as self-reported in REACH dossiers) and those currently in place as identified through questionnaire responses. We used the following sources:

- Questionnaire responses;
- REACH registration dossiers.
- Relevant data from Annex XV dossiers, RAC/SEAC opinions, articles and reports and association websites; and
- Safety Data Sheets supplied to downstream users by manufacturers.

241 https://newsletter.echa.europa.eu/home/-/newsletter/entry/healthy-workplaces-knowing-and-controlling-the-risks-of-dangerous-substances Accessed 27 November 2018

X7.2.2 Summary of recommended RMMs identified

Information on the specific RMMs identified here for the shortlisted substances from Task 2.3 are discussed in Annexes 10-21. An overview of available information on RMMs is also presented for those substances that are classified Repro. 1A/1B but not shortlisted.

Table X7-1 provides a summary of the REACH recommended RMMs by substance, including the 3 aprotic solvents. By definition, these REACH recommended RMMs relate to uses of the substance and therefore do not include substitution. As the substances are Repro. 1A/1B and not also Carc. or Mut. 1A/1B, one would expect the measures to focus on designing out exposures followed by adoption of appropriate organisation and other measures, basically the TOP part of the STOP hierarchy. As can be seen from Table X7-1, a number of measures are specified as RMMs within the REACH dossiers, starting with use in a closed system, followed by organisational measures, other managerial measures, and personal protective equipment (PPE) measures all consistent with the CAD.

From the dossiers it is also clear that there is often a hierarchy in these recommendations, with Local Exhaust Ventilation (LEV) or adequate ventilation to remove or prevent exposures generally given priority to the use of respiratory protection equipment (RPE). Using proper Industrial Hygiene principles, PPE should always be the tool of last resort. This is consistent with CAD, as are the recommendations for other measures aimed at preventing or reducing exposures (e.g. protective clothing or boots). It is not clear that the recommendations give sufficient priority to technical and organisational measures compared to the use of personal protective equipment (PPE/RPE).

X7.2.3 RMMs in Safety Data Sheets

Interestingly, Safety Data Sheets provided by suppliers sometimes (often?) go beyond the RMMs recommended in the REACH registration dossier[242]. Of particular note is that some of the SDSs stress the need for employers to undertake a risk assessment and to select the level of control required on the basis of this, for example, where some form of RPE is recommended. Within the context of this study, this is an interesting finding as it demonstrates that suppliers also communicate the importance of an own risk assessment to employers, in line with CAD. It means however that everyone will need to do a risk assessment which appears not to be in accordance with CAD and will unevenly burden SMEs.

[242] Please note that further enhancement to SDS's will occur with deployment of e(xtended)SDS's – we were unable to locate more than one (DMAC) for our 31 chemicals as of 24 November 2018.

Table X7-1: Recommended RMMs for borates from REACH registration information															
Substance	**Measure**	**Substances**													
		Borates	**Dodecyl compounds**	**Lead compounds**	**Retinol**	**Tins**	**BPA**	**Dinoseb**	**Imidazo-lidine-2-thione**	**4-tert-butylbenzoic acid**	**2-ethoxy-ethanol**	**DMF**	**NMP**	**DMAC**	**THTO**
Closed systems/ engineering controls	Use in a closed-system		✓	✓		✓	✓	✓	✓	✓	✓				
	LEV for ensuring airborne concentrations are below permissible exposure limits	✓				✓						✓?			✓
	Sufficient ventilation to remove and prevent build-up of vapours, dusts or fumes that could be generated during handling or thermal processing	✓	✓				✓	✓		✓	✓	?			
Organisational measures	Handle in accordance with good industrial hygiene and safety practice														
	Procedural and/or control techniques to minimise exposure during cleaning and maintenance and where the OEL may be exceeded				✓										
	Avoid contact with eye, skin and inhalation						✓		✓				✓	✓	
	Do not eat or drink; do not smoke when using the substance,		✓	✓		✓		✓			✓				✓
	Wash hands before breaks and at the end of the work day		✓	✓					✓	✓	✓				✓

Table X7-1: Recommended RMMs for borates from REACH registration information															
Substance	Measure	Substances													
		Borates	Dodecyl compounds	Lead compounds	Retinol	Tins	BPA	Dinoseb	Imidazo-lidine-2-thione	4-tert-butylbenzoic acid	2-ethoxy-ethanol	DMF	NMP	DMAC	THTO
	Requirements for storage rooms and vessels; storage room floor must be impermeable to prevent escape of liquids			✓				✓							
	Keep working clothes separate; vacuum clean contaminated clothing; take off contaminated clothing immediately			✓						✓	✓			✓	
	Obtain special instructions before use			✓											✓
	Keep away from foodstuffs, beverages, and feed			✓						✓	✓				
	Workplace should be cleaned after every shift (e.g. HEPA vacuuming)			✓						✓					
	PPE to be determined by a qualified person		✓				✓					✓			
Respiratory protection	Respirators should be used (CEN 143 or 149) where the airborne concentrations are expected to exceed the exposure limit	✓		✓	✓	✓		✓			✓	✓	✓	✓	✓
	Wear respirator with dust filter; Air purifying respirator	✓	✓						✓	✓					

Table X7-1: Recommended RMMs for borates from REACH registration information															
Substance	**Measure**	**Substances**													
		Borates	**Dodecyl compounds**	**Lead compounds**	**Retinol**	**Tins**	**BPA**	**Dinoseb**	**Imidazo-lidine-2-thione**	**4-tert-butylbenzoic acid**	**2-ethoxy-ethanol**	**DMF**	**NMP**	**DMAC**	**THTO**
Eye protection	Eye protection is required (CEN 149); dust proof or appropriate goggles	✓			✓					✓					
	Showers and eye wash station	✓													
	Face shield for splash hazards; Safety glasses with side shields		✓		✓	✓	✓	✓				✓	✓	✓	
	Eye protection/ Chemical googles as per a health and safety professional (OSHA (29 CFR 1910.133) or EN166 (Europe))		✓	✓		✓	✓				✓	✓	✓	✓	✓
Skin and body protection	Protective clothing and shoes/boots	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓			
	Wear gloves (rubber, nitrile, butyl) if dusty	✓	✓			✓			✓						
	Impervious / protective gloves for prolonged contact (including instructions to wear other types than rubber gloves)		✓	✓	✓		✓	✓		✓	✓	✓	✓	✓	✓
Source: Annexes 10-21															

More generally, there is also coherence between the measures recommended to users of the substances with what would also be required under the CMD, although of course the eSDS do not recommend substitution.

X7.2.4 Comparative analysis of Dossier and eSDS requirements

Mention has been made of the discrepancies between the (PPE and RMM) requirements in the ECHA Registration Dossier and what is eventually listed on the (e)SDS. These discrepancies are not minor and indicate to what extent companies cannot rely on the dossiers for the listed RMMs (as was the intent of these dossiers) but must follow the more extensive (and expensive) requirements laid out in the (e)SDS. It appears some companies have taken the "check all the boxes just in case" approach for the preparation of the (e)SDS. Especially for SME's this makes it even more imperative to maintain a full up-to-date library of SDS and related material. On the other hand the argument could be made that the eSDS does not require a company/SME to maintain a cadre of experienced occupational health specialists, except (defeating that advantage is) that the requirement for most of the chemicals is that a site-specific risk assessment still needs to be performed, requires at a minimum contracting for these services.

In Table X7-2 we have provided a comparative analysis of the SDS and dossier requirements for DMAC (e SDS). The compound was picked as an example of an eSDS. (An analysis of all available SDS's for our 30 chemicals is beyond the scope of this project.) As can be seen, the dossier requirements are less restrictive/extensive than the eSDS. Whether this reflects better judgment on RMMs on the part of the manufacturing facility or an attempt to minimize liability, is up to the reader to decide. Note the massive discrepancy re firefighting procedures: the dossier recommends water spray, the eSDS rejects it.

Extrapolating from this case study it appears obvious that RMM measures on the SDS are "overprescribed" beyond the initial requirements detailed in the registration dossier. It is unclear how much more, but clearly compliance with the SDS requirements is more expensive than specified by the original dossier. Its economic impact on industry, especially SME's, remains hard to quantify, but does not appear to be inconsequential.

These instances are not just limited to DMAC. SDS's (e.g. for disodium tetraborate, anhydrous) may also state that technical measures and appropriate working operations should be prioritised over the use of PPE and to use respiratory protection where dusts are generated[243] again similar to STOP principles. Similarly, the SDS's for Imidazo-lidine-2-thione and 4-tert-butylbenzoic acid state, for example, that where the employer's risk assessment shows that air-purifying respirators are appropriate, a full-face particle respirator type P3 (EN 143) with respirator cartridges should be used as a backup to engineering controls. If respiratory equipment is the only mean of protection, then the use of a full-face supplied air respirator is recommended.

The interpretation of these data is overwhelming for untrained personnel, especially the resolution of apparently conflicting statements, thereby to some extent defeating the (original) purpose of an SDS, communicating health information in an understandable format. This in turn will necessitate further training, most often by outside contractors in the case of SMEs.

[243] Merck (2017): Disodium tetraborate, anhydrous Safety Data Sheet. Available at: http://www.merckmillipore.com/INTERSHOP/web/WFS/Merck-GB-Site/en_US/-/GBP/ProcessMSDS-Start?PlainSKU=MDA_CHEM-106306&Origin=PDP

Table X7-2: DMAC- Comparative overview Dossier vs SDS [244]		
Category	**Dossier[245]**	**SDS[246]**
Use	Use as laboratory reagent,	
Hazard Categories	H312, H332, H360D (However H319 is also reported by some of the Notifiers)[247]	H312, H332, H319, H360D
Firefighting	a) Suitable extinguishing media: water spray, dry powder, foam, carbon dioxide	a) Suitable extinguishing media: Carbon dioxide (CO2), Dry chemical, Alcohol-resistant foam b) Unsuitable extinguishing Media: Water spray jet
Handling	Ensure thorough ventilation of stores and work areas. Product should be worked up in closed equipment as far as possible.	Handle in accordance with good industrial hygiene and safety practice. Keep product and empty container away from heat and sources of ignition.
Storage	Segregate from strong oxidizing agents. Keep container tightly closed and in a well-ventilated place. Avoid extreme heat. Keep away from sources of ignition - No smoking	Keep container tightly closed in a dry and well-ventilated place.
Engineering measures	None listed	Good general ventilation (typically 10 air changes per hour) should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation, or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.
Eye protection	Safety glasses with side-shields (frame goggles)	Safety glasses with side-shields; Face-shield
Hand protection	Chemical resistant protective gloves (EN 374) Suitable materials also with prolonged, direct contact (Recommended: Protective index 6, corresponding > 480 minutes of permeation time according to EN 374): butyl rubber (butyl) - 0.7 mm coating thickness	Rubber gloves/Neoprene gloves

[244] Information not listed in this table are similar/comparable in Dossier and SDS.

[245] https://echa.europa.eu/registration-dossier/-/registered-dossier/15266 accessed 24 November 2018

[246] https://ws.eastman.com/ProductCatalogApps/PageControllers/MSDSShow_PC.aspx accessed 24 November 2018 eSDS?

[247] https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/116425

X7.2.5 Additional RMM identified by industry consultees

Consultation responses indicate that the measures actually in place are in compliance with REACH dossier and eSDS but as we have seen the (e)SDS are often way more stringent than the REACH dossier requirements. Even so some companies feel the need to go beyond the eSDS in their RMMs. In particular, additional "elimination" and "organisational measures" have been implemented by employers that go beyond what is required of them.

Examples of additional RMMs include:

- Use of automated systems for the delivery of the hazardous substance;
- Use of glove boxes;
- Restricting access to areas where Reprotoxic 1A/1B substances are used to authorised workers only;
- Requiring the separation of work and personal clothing, with the provision of personal storage cupboards
- Introducing a range of hygiene measures, such as no eating and drinking and on-site washing facilities;
- Safety cards and photographs to demonstrate safe use.

The consultation responses are mainly from medium and large-sized enterprises, however, there are some responses from small enterprises (less than 50 employees). Across the range of consultation responses, it is clear that many employers do give consideration to the STOP hierarchy and identify their own measures based on the outcome of a specific risk assessment.

Interestingly, many of the companies also identified measures that would also be consistent with application of the hierarchy under CMD such as hazard-based substitution and use of technical measures to control exposures.

X7.2.6 Relevance of other classifications

As well as being classified as Repro 1B, several of the substances also have classifications for other hazards which result in the need for specific risk management measures. For example, Phenol, dodecyl-, branched and Phenol, dodecyl-, sulfurized, carbonates, calcium salts as well as being classified as Repro 1B, are also classified as a Skin Corr. 1C (H314) and Eye Dam. 1 (H318); the recommended risk management measures therefore also take into account such exposures.

X7.3 Best practice examples

X7.3.1 Introduction

For the purposes of this assessment, we have defined 'best practice' as reflecting cases where companies have put in place processes which reflect the requirements of the CAD and/or CMD (and potentially go further) with the aim of ensuring that occupational exposures are sufficiently controlled, i.e. (well) below current occupational exposure limits. We have therefore looked for examples providing evidence that the "STOP principle" is adhered to. In this respect, we have treated elimination as being equivalent to substitution.

The focus has been on identifying examples from targeted consultation. In some cases, the measures actually in place are driven by participation in voluntary industry initiatives (e.g. for lead), with these reflecting what is considered at the sectoral level as being "best practice". Responses to the

consultation include companies that are members of the International Lead Association's Blood Lead Reduction Programme. Further details of this initiative are given in Annex 8, and consultation responses demonstrating compliance with this initiative are not detailed below. Instead, we have pulled out examples from a range of other responses which relate to the use of different Repr. 1A/1B substances, as well as company size and sector of activity.

It is generally not possible to determine from the consultation responses what the motivating factors were for the measures adopted by companies, although there are some cases where companies note that their policy is to eliminate exposures to hazardous substances wherever feasible. We have identified these companies as examples of best practice, together with others that have taken a range of measures in line with the STOP principle.

There are also examples from substitution initiatives and the literature which illustrate the potential for chemicals substitution. For example, there are numerous examples on SUBSPORT – the Substitution Support Portal[248] - which relate to substitution of reprotoxins; other examples will exist in TURI[249] . A few examples are provided below, where these appeared to be driven by a desire to reduce worker exposures as by other regulatory pressures or an attempt to capture market share by responding to consumer pressures. It is important that this broader context is recognised, as many of these examples will not have been driven by employers' consideration of their Occupational Safety & Health (OSH) obligations, but by market supply and demand considerations.

X7.3.2 Basis for identifying best practice examples

Responses to the targeted consultation were received from over 40 individual companies. As part of this consultation, companies were asked not only to identify what Repro. 1A and 1B substances they used, but also what risk prevention and risk management measures they took with respect to worker exposures. The relevant questions were as follows:

a) Has your company made use of the 'slight risk' rule under the CAD?

b) Has your company carried out any activities with regard to **the replacement** of the relevant substance(s)? If YES, did these activities stem from a determination of a risk in a risk assessment (with the exception of a slight risk) or were they carried out independently of a risk assessment? Please also specify the relevant activities.

c) Has your company carried out any activities with regard to **prevention and reduction of exposure (collective measures)**? Examples of collective measures include closed systems, ventilation, etc. If YES, did these activities stem from the determination of a risk in a risk assessment (with the exception of a slight risk) or were they carried out independently of a risk assessment? Please also specify the relevant activities.

d) Has your company carried out any activities with regard to **restricted access to risk areas**? Examples of relevant measures include demarcation of the relevant areas and restricted access to authorised workers. If YES, did these activities stem from the determination of a risk in a risk assessment (with the exception of a slight risk) or were they carried out independently of a risk assessment? Please also specify the relevant activities.

[248] https://www.subsport.eu/

[249] Toxics Use Reduction Institute. See for examples of alternatives assessments highlighting the potential for substituting hazardous chemicals, including reprotoxins such as lead and phthalates: https://www.turi.org/Our_Work/Research/Alternatives_Assessment/Examples

e) Has your company carried out any activities with regard to **health surveillance/monitoring**? If YES, did these activities stem from the determination of a risk in a risk assessment (with the exception of a slight risk) or were they carried out independently of a risk assessment? Please also specify the relevant activities.

f) Has your company carried out any activities with regard to **planning for unforeseen/accidental exposure**? If YES, did these activities stem from the determination of a risk in a risk assessment (with the exception of a slight risk) or were they carried out independently of a risk assessment? Please also specify the relevant procedures in place for such events.

g) Has your company carried out any activities with regard to **personal protection measures**? These may include, for example, the provision, specification, maintenance and storage of personal protective equipment (PPE)), etc.

h) Has your company carried out any activities with regard to **personal hygiene** requirements (e.g. no eating/smoking/drinking, separate storage of work and street clothes, washing/toilet facilities, etc.)?

i) Has your company carried out any activities with regard to **the provision of information/training to workers and their participation in decision making**?

j) Have you implemented any additional measures that are relevant to reprotoxic substances (e.g. regarding the **protection of pregnant women, breastfeeding mothers and young people**)?

k) Has your company carried out any activities with regard to **record keeping and provision of information to the authorities**?

Examples of "best" or "good" practice have been pulled out of individual companies responses. These are summarised below, with a focus on the most informative aspects of individual responses.

X7.4 Examples from consultation

Company A

Company A is located in Germany and identified itself as a user of *"Other Cat 1A and 1B Reprotoxins"*. It is a large enterprise employing more than 250 persons involved in the "manufacture of paints, varnishes and similar coatings, printing inks and mastics" (NACE code C20.3).

They undertake the constant review and substitution of reprotoxic substances to ensure that the number of workers exposed will be reduced over time. Process and decision making concerning risk management is now centralised, so that individual sites cannot introduce hazardous substances in isolation. Any such requests need global senior management approval and for reprotoxins this would only be given in very special circumstances; the use of no new reprotoxins has been approved to date.

As part of corporate risk management, substitution has been completed for "some or all" of the relevant reprotoxins. The company is undertaking an "ongoing process of substitution of such materials in line with CMR and OHS/ sustainability targets". Where substitution has not yet been feasible then "all such materials are either reduced to as low as reasonably practicable via dedicated

equipment, LEV and or PPE in line with CAD (and CLP) requirements. PPE is managed via a matrix system which applies to the use of all substances, in line with CLP guidelines. Policies and procedures are also in place for emergency preparedness in the event of an emergency (hospitals, etc), with these activities linked to determination of a potential risk from the risk assessment.

The company's health and safety policies include specific measures to restrict the access of "susceptible" workers to high risk areas. (Risk assessments have been carried out on relevant substances and restrictions put in place.) For example there is the prohibition of certain individuals to areas where materials may pose a particular threat (e.g. pregnant women). Health surveillance processes are in place for various worker safety issues, with these generally carried out annually; but, where required, the frequency can be increased.

With respect to information provision/training or the participation of workers in decision making, this company notes that they have a full consultation process in place, in line with union / management regulations. More generally, there is a full European works council in place to allow such communication to take place and representation on management teams at group level for union members.

Company B

Company B is located in Italy and identified itself as a user of *"Other Cat 1A and 1B Reprotoxins"* when responding to the questionnaire. It is a medium-sized enterprise (50-249 persons employed) involved in the "manufacture of pesticides and other agrochemical products" (NACE code C20.2). All four of the substances identified by Company B are approved active substances under the Biocidal Products Regulation.

The company has not considered substitution for these per se at this time, which is not surprising given that these substances are being used as active ingredients regulated under the Biocidal Products Regulation and in some cases the Plant Protection Products Regulation. All of the identified substances were recently (2017) given harmonised classifications as Repro. 1A/1B under the CLP and, although they are currently approved, they meet the exclusion criteria and are candidates for substitution as R (unless derogated, e.g. for essential uses).

Collective measures have been implemented with regard to the prevention and reduction of exposures. For example, worker exposures may occur when operators are pre-weighing the active ingredient (i.e. one of the reprotoxins currently being used). Such operations are carried out inside a dedicated room under continuous ventilation, with exposures limited to one hour per day or less. Even so, the company notes that the possible inclusion of the reprotoxic chemicals 1A and 1B in the Directive on Carcinogens and Mutagens would inevitably lead to a significant change in the production risk management system associated with significant investments.

With respect to organisational measures, the company has established some general rules:

- No eating & drinking in the production area;
- It is forbidden to smoke in the production area;
- Suitable areas are provided for taking breaks and for consuming food outside the production area;
- For all production operators there are available changing room (male and female) with a wardrobe for each employee, to enable production clothing to be kept separate from clean clothes; and
- In the changing room, there are several showers that can be used by any employee at the end of the shift.

The company implemented a PPE matrix based on a risk assessment The PPE matrix is shared with employees (properly trained on this aspect) in order to ensure that everyone use the right PPE during the several phases of the process. All employees have received training for at least 16 hours touching also chemical aspects and Specific Chemical Risk Assessment.

A physician, based on the chemical risk assessment, prepared a medical monitoring protocol for the production operators. As a result, the company carries out biological monitoring once a year to test blood levels for two different biomarkers. Note that this information is for internal use and does not form part of recordkeeping for provision to authorities.

In addition, when the substances were given new harmonised classifications for Reprotoxic 1A/1B substances, all female employees were informed. The risk assessments for the substances were updated with specific regard to the case of pregnant workers. Any pregnant worker will be removed from activities where contact with the active substances is possible (although no female workers are currently involved in formulation activities where the substances are present).

Finally, the company has in place an Emergency Plan Document where it is possible to find information about "Spill Response Procedure". The Emergency Plan is tested with a “real case performance test” at least once per year.

Company C

Company C is a warehousing company linked to a non-EU borates manufacturer, with facilities in Luxembourg and Finland. It is a large company in terms of turnover but not in terms of the number of employees. Worker exposures may occur during: warehouse operations, unloading the product (bulk/bagged) from vessels/containers, storing the products in the warehouse, handling the products (cutting bags - debagging -, delumping, sieving, re-bagging), loading the product into trucks/silo-trucks. Across all warehousing operations within the EU between 50 to 100 employees may be exposed.

The company undertakes dust monitoring within its warehouses (and has provided monitoring data for use in this study). The monitoring results have been used as the basis for undertaking improvements in worker protection, and reductions in inhalable dust levels have already been achieved. Dust monitoring campaigns are undertaking periodically and are shared with the upstream sector association so that the results can feed into updates of the manufacturers exposure scenarios (and hence registration dossiers). Most if not all of the workers are males (with another warehousing respondent indicating that pregnant women, breastfeeding mothers and underage people are not allowed in the plant).

In this case, substitution is not relevant, but the company notes that measures were introduced well before the harmonised classification for the Reprotoxic 1A/1B substance came into force. The company has implemented collective measures aimed at reducing worker exposures based on risk assessments. These include the introduction of local exhaust ventilation and dust collectors. In terms of access restrictions, these are in place for all of the relevant substances, and include the use of signage over the entrances of bulk storage areas, with some stations only open to authorised workers. With respect to PPE, employees are equipped with overalls, safety shoes, gloves, safety googles, and respirators (P2/P3). All workers are instructed to follow information on the SDS with respect to good hygiene practice, e.g. do not eat, drink or smoke during work time; keep away from foodstuffs and beverages; wash hands before breaks and after work; remove contaminated clothes and protective equipment before entering eating area.

Workers training includes the provision of written operation manuals and technical guidance, as well as the use of face-to-face training courses and internal meetings.

Company D

Company D is a large chemicals manufacturer located in Belgium, whose activities include the use of a range of Reprotoxic 1A/1B substances, including substances prioritised for this study and additional substances. The company is a member of the Responsible Care® initiative (see also voluntary initiatives).

The starting point for this company is that the frequency and duration of exposures must be reduced to be as low as is achievable. The company's policy is to substitute and/or reduce the exposure to Repro. 1A/1B substances based on the identification of CMR substances (searching of inventories), through searches for safer alternatives (elimination, substitution, change of the physical state), and through adoption of specific RMMs. All RMMs must be technically and economically feasible, however, they would never apply the "slight risk" rule available under CAD for Reprotoxic 1A/1B substances. The site is certified according to OHSAS 18001:2007.

Looking for substitution possibilities is a prerequisite of the company policy before carrying out a risk assessment for all activities (production, lab activities (QC and R&D), maintenance). The hierarchy of risk controls in the STOP approach is followed.

The use of closed systems and ventilation are examples of collective measures which have been installed at the facility. Procedures are also in place to cover the provision, specification, maintenance and storage of personal protective equipment (PPE). All workers have been trained. At all points; where exposure is possible, there is a visual aid in which the PPEs to be worn for the operation are photographed and displayed. Information and training for workers is carried out at all sites. The participation of workers in the decision making is strongly encouraged but application can vary between sites.

In the event of an unforeseen/accidental exposure, workers have to contact the occupational physician for a medical examination. Situations leading to such an unforeseen/accidental exposure are assessed in order to improve the protective measures in place.

Areas where Reprotoxic 1A/1B substances are used/stored are usually marked with pictograms and sometimes restricted access is put in place. Pregnant or breastfeeding women are forbidden to access areas where there is the potential for exposure to Reprotoxic 1A/1B substances. Mandatory minimum requirements regarding maternity protection are also in place, including risk assessment, information to the workers and avoiding exposure to reprotoxic substances.

Interestingly, the company undertakes biological monitoring for a range of substances, including Repros. 1A/1B substances, Cat. 1A/1B carcinogens, other chemical agents, and substances that are subject to REACH or other restrictions but that are no longer used (and which do not have mandatory biomonitoring requirements). Air measurements are also undertaken with all results below the occupational exposure limits. Records are kept of medical data and exposure data across all sites and in relation to all substances monitored for (thus including Repros. 1A/1B). This information is provided to authorities when requested.

Company E

Company E is located in Denmark and is a large enterprise within the chemicals manufacturing sector (NACE C20). They are a member of the CEPE (CEFIC) Product Stewardship initiative to minimize the use of hazardous raw materials. They have identified over 10 Repro 1A/1B substances as being of relevance to their activities, including some of the substances being examined in more detail for this study.

Worker exposures may include during 1. Picking raw materials; 2. Loading raw materials into vats; 3. Mixing in vats; 4. Transfer; 5. Filling; and 6. Laboratory analysis. Up to 300 workers may be exposed while undertaking the first 5 of the above activities, while a further 50 workers are potentially exposed as part of laboratory analyses. The maximum durations of exposures are estimated at up to 4 hours per day, with these being relevant to loading and filling operations, which are undertaken under local exhaust ventilation. All other activities involve exposures of less than an hour per day.

The company undertakes biological monitoring (blood, urine) as a general health check, but not specifically for reprotoxins. Workplace air monitoring is undertaken for a subset of the substances at present. Health surveillance is carried out for all production workers (bi)annually.

The company is currently in the process of running a hazard based substitution programme for all CMR substances. Where substitution is not possible, a risk assessment is carried out to ensure safe use in their manufacturing and at customers' facilities. All of their production processes have been risk assessed. Automatisation of their factories, will minimize exposure. For example, dosing of solvents is now carried out automatically via pipes. Exposure only occurs when opening the vat for loading other raw materials. Local exhaust ventilation is installed in filling lines, where the lines have not been fully automated. Interestingly, they are also developing high solids products, to minimize the use of solvents which are Repro 1A/1B, within their processes.

They have standard general safety practices to minimize exposure to chemicals, including restricted access to production areas and laboratories. Toxic chemicals are stored separately. A work place safety card is made for every raw material, indicating which PPE to use during handling. All workers have been trained in use of PPE. In addition, for all of the processes described above, organisational measures apply, such as: No eating, drinking or smoking; Separate storage of work and street clothes; Bathing facilities available at all sites, etc.

All production workers have been trained in chemical risks, prevention of accidents and the use of PPE. All new staff go through an induction training on site. A safety campaign is currently running including the possibility to contribute new ideas for improved/safer processes. General emergency procedures are in place for fires and spillages, with the potential for a fire considered to be a bigger risk to workers than exposure to toxic and CMR substances.

The company does not employ anyone below the age of 18 years. Pregnant women are transferred to a work setting without exposure to reprotoxic chemicals.

X7.4.1 SUBSPORT examples

Example 1: a potential alternative to the use of Bisphenol A as a colour developer in thermal paper

In 2010, the Jegrelius Institute published a report indicating that the high levels of BPA contained in receipts may pose a health hazard for cashiers and others working with such receipts on a daily basis. One of the companies found to be using bus tickets containing high levels of BPA (a regional transport company) wanted to substitute their receipts with a BPA-free alternative. This company is said to have been motivated by the potential risk to their employees who handle large quantities of bus tickets.

A project was subsequently launched by the Jegrelius Institute in 2011 to evaluate several alternatives to BPA (Bisphenol A) as a colour developer in thermal paper. The aim was to identify available alternatives that result in fewer impacts on human health and the environment. A single likely alternative candidate, Pergafast 201, was identified.

Due to reasons of confidentiality, the Institute was not able to obtain specific information on the alternative that was used in place of BPA by the regional transport company. For this reason, the first approach to identifying alternatives was to draw up a list based on the alternatives listed by the United States Environmental Protection Agency (EPA) initiative – BPA Alternatives in Thermal Paper Partnership. From this list it was possible to identify an alternative matching the information that was provided on the substitution, Pergafast 201. This is the only alternative manufactured on a large scale, that is not simply another variant of bisphenol.

BPA is classified as R37 (irritating to respiratory system), R41 (risk of serious damage to eyes), R43 (may cause sensitisation by skin contact), R62 (possible risk of impaired fertility) and R52 (harmful to aquatic organisms), while Pergafast 201 has only currently been classified as R51/53 (Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment).

It was concluded that although Pergafast 201 could be dangerous if released into the aquatic environment, due to the manner in which receipts are handled, the majority are unlikely to reach the aquatic environment and this is therefore considered an acceptable risk. [250]

Example 2: SUBSPORT Specific Substances Alternatives Assessment for the use of lead as a thermal stabiliser in the production of PVC

Lead was used as a thermal stabiliser in the production of polyvinyl chloride (PVC). Thermal stabilisers are used in polymers to prevent effects such as oxidation, chain scission and 'uncontrolled' recombinations and cross-linking reactions that are caused by photo-oxidation of polymers. Without such stabilisers the material would weather under the direct or indirect impact of heat and ultraviolet light.

This assessment reviewed the hazard characteristics of the following possible alternatives:

- Calcium-zinc stabiliser
- Magnesium aluminium hydroxide carbonate hydrate stabiliser
- organotin stabiliser.

[250] Substitution Support Portal (SUBSPORT) Website (2011): 'A potential alternative to the use of Bisphenol A as a colour developer in thermal paper', accessed on 14/08/18 at: https://www.subsport.eu/case-stories/164-en

The hazard characteristics assessed included physical hazards such as explosivity, flammability, and oxidizing, human health hazards such as acute toxicity, skin or eye corrosion/irritation, carcinogenicity, mutagenicity, reproductive toxicity, endocrine disruption, respiratory or skin sensitization, neurotoxicity, immune system toxicity, systemic toxicity and toxic metabolites, as well as environmental hazards such as acute/chronic aquatic toxicity, bioaccumulation, persistence, greenhouse gas formation potential, ozone-depletion potential and monitoring (has the substance been found in human or environmental samples?).

The assessment carried out by SUBSPORT in 2013 concluded that the 'calcium-zinc and hydrotalcite stabilisers are confirmed to be environmentally-friendly and effective additives for PVC. They are better alternatives with regard to human health than lead and tin stabilisers.'[251]

In 2000, ESPA (the European Stabiliser Producers Association) committed to replacing lead-based stabilisers by the end of 2015 across the EU, and by the end of 2015, ESPA members had indeed replaced their lead-based stabilisers in 'all their formulations sold in the EU-28 market.' This took place as part of the Voluntary Commitment of the European PVC industry to sustainable development, first under 'Vinyl2010' and then the 'VinylPlus Programme'.[252]

Example 3: Substitutions performed at the National Centre for Health Data and Disease Control in Denmark (SSI)

SSI carries out advanced diagnostics, health data analysis and vaccine production. A significant proportion of their diagnostic activities involve gel electrophoresis of DNA, RNA and proteins, which includes handling of 'gel and running buffers' containing boric acid.

Boric acid can potentially harm an unborn child and impair fertility and substitution was driven by the fact that the majority of the laboratory staff were women, with many between the age of 20 and 45. A substitution based on acetic acid was identified, and although acetic acid is flammable (R10) and causes severe burns (R35), it does not harm an unborn child or impair fertility.

In most cases it has been possible for SSI to substitute their buffer containing boric acid (TBE-buffer (tris(hydroxymethyl)aminomethane, boric acid, EDTA)) with a buffer containing acetic acid (TAE-buffer (tris(hydroxymethyl)aminomethane, acetic acid, EDTA)). In some rare cases the buffer containing acetic acid reduces band resolution and the boric acid containing buffer must be used instead, otherwise this use of boric acid has 'dropped to a minimum'.[253]

[251] Substitution Support Portal (SUBSPORT) Website (2013): 'SUBSPORT Specific Substances Alternatives Assessment – Lead and its inorganic compounds', accessed on 14/08/18 at: http://www.subsport.eu/wp-content/uploads/data/lead.pdf

[252] European Stabiliser Producers Association (ESPA) website (unknown): 'Lead Replacement', accessed on 14/08/18 at: https://www.stabilisers.eu/lead-replacement/

[253] Substitution Support Portal (SUBSPORT) Website (2012): 'Substitutions performed at the National Centre for Health Data and Disease Control in Denmark (SSI), accessed on 14/08/18 at: https://www.subsport.eu/case-stories/208-en

X7.5 Substance Specific RMMs

X7.5.1 Borates

REACH measures

The shortlisted borates (as part of task 2.3) are: boric acid; disodium tetraborate, anhydrous; diboron trioxide; perboric acid, sodium salt; and disodium octaborane. Risk management measures for the borate substances as recommended from REACH registration information are summarised in the following table.

Borate substances have been registered under REACH for a wide variety of uses. For examples, PROC codes 1-26 are relevant for boric acid. PROC codes where exposure could occur for boric acid include:

- PROC 4 (Chemical production where opportunity for exposure arises);
- PROC 7 (Industrial spraying);
- PROC 10 (Roller application or brushing);
- PROC 15 (Use as a laboratory reagent); and
- PROC 26 (Handling of solid inorganic substances at ambient temperature).

For the borate substances, the recommended risk management measures are similar for each borate substance. Respiratory protection is recommended with dust proof goggles also listed (as eye protection). Protective clothing is also recommended, with showers and eye wash stations.

Safety data sheets

Measures for reducing exposure to boric acid are also provided by suppliers to their downstream users through Safety Data Sheets (SDS). These list control parameters (components with workplace control parameters), appropriate engineering controls, eye/face protection, skin protection, body protection and respiratory protection recommended for handling the substance.

The recommended exposure controls are similar to those recommended in the Registration dossier with some additional measures recommended. By way of example, for boric acid, the additional measures listed are: [254]

- Eye protection (Safety glasses with side shields- EN166) is recommended;
- Impervious clothing is recommended for body protection;
- Respiratory protection recommended is to use a full face particle respirator type P3 (EN 143) respiratory cartridges as a backup to engineering controls; and
- Where there are no controls, a full-face supplied air respirator is recommended.

[254] Sigma Aldrich (2017): Boric acid Safety Data Sheet. Available at: https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=185094&brand=ALDRICH&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2F185094%3Flang%3Den

Table X7-3: Recommended RMMs for borates from REACH registrations		
Substance	**Measure**	**Details**
Boric acid	Organisational measures	Ensure adequate ventilation; LEV for ensuring airborne concentrations are below permissible exposure limits
	Respiratory protection	Respirators should be used (CEN 149) where the airborne concentrations are expected to exceed the exposure limit
	Skin and body protection	Wear gloves (rubber, nitrile, butyl) if dusty
Disodium tetraborate, anhydrous	Organisational measures	Ensure adequate ventilation; LEV for ensuring airborne concentrations are below permissible exposure limits
	Respiratory protection	Respirators should be used (CEN 149) where the airborne concentrations are expected to exceed the exposure limit
	Skin and body protection	Eye protection is required (CEN149); Wear gloves (rubber, nitrile, butyl) if dusty
Diboron trioxide	Organisational measures	Ensure adequate ventilation; LEV for ensuring airborne concentrations are below permissible exposure limits
	Respiratory protection	Respirators should be used (CEN 149) where the airborne concentrations are expected to exceed the exposure limit
	Skin and body protection	Wear gloves (rubber, nitrile, butyl) if dusty
Perboric acid, sodium salt	Organisational measures	Adequate ventilation
	Respiratory protection	Wear respirator with dust filter
	Eye protection	Dust proof goggles
	Skin and body protection	Protective clothing and shoes; rubber gloves
	Other	Showers and eye wash stations
Disodium octaborane	Organisational measures	Ensure adequate ventilation; LEV for ensuring airborne concentrations are below permissible exposure limits
	Respiratory protection	Respirators should be used (CEN 149) where the airborne concentrations are expected to exceed the exposure limit
	Skin and body protection	Wear gloves (rubber, nitrile, butyl) if dusty
Sources: ECHA (2018): Boric acid REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15472/9 ECHA (2018): Disodium tetraborate, anhydrous REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15357/9 ECHA (2018): Diboron trioxide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15317/9 ECHA (2018): Perboric acid, sodium salt REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/13523/9 ECHA (2018): Disodium octaborane REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14136/9		

Interestingly, the safety data sheet for disodium tetraborate, anhydrous states that technical measures and appropriate working operations should be prioritised over the use of PPE (in concordance with proper IH management) and to use respiratory protection where dusts are generated.[255]

[255] Merck (2017): Disodium tetraborate, anhydrous Safety Data Sheet. Available at: http://www.merckmillipore.com/INTERSHOP/web/WFS/Merck-GB-Site/en_US/-/GBP/ProcessMSDS-Start?PlainSKU=MDA_CHEM-106306&Origin=PDP

Consultation Responses

Risk management measures that are in place in companies for reducing workplace exposure to borates are discussed in the following tables. The processes that the substances are used for and also exposure concentrations are discussed which illustrates the effect of risk management measures on workplace exposure. Generally, risk management measures for borates:

- Involves the use of closed systems and other measures if necessary;
- Separation of work and personal clothing;
- Involves hygiene measures, such as no eating and drinking;
- Exposure duration varies from a couple of minutes to a full work shift; and
- Involves the use of PPE for workers.

Exposure concentration measurements are limited, with exposure concentrations ranging from <Limit of Detection (LOD) to 0.72 mg/m^3 reported from consultation with RMMs put in place for these measurements.

Table X7-4: RMMs used for the handling of borates by companies

Substance	Operation	RMMs used	Other practices	Exposure (duration, concentration)
Borates	Electroplating; metallisation; soldering; production line operators; maintenance workers	Restricted areas; PPE classified by the work place and standard	No eating, drinking and smoking at the work site; separate storage of work and personal clothing; workers complete chemicals safe handling course	7.5 hours a day for production operators; 1 hour a day for maintenance workers H_3BO_3 exposure level is below the detection level
Boric acid	Manufacturing of fertilisers	PPE; standard operating procedures; SDS; Labelling	-	-
Boric acid; disodium tetraborate anhydrous; disodium octaborane	Manufacture of other basic inorganic compounds	P2 or P3 face masks (compulsory for some operations);	No eating, drinking and smoking on site; separate storage of work and personal clothing; SDS are used; on site washing facilities	6-7.5 hours per day for 5 days a week
Diboron trioxide; disodium tetraborate, anhydrous	Manufacture of other inorganic basic chemicals Mining of chemical and fertiliser minerals • Warehousing and storage •	P2 or P3 PPE used (compulsory for some activities);	No eating, drinking and smoking on site; separate storage for work and personal clothing; on site washing facilities; periodic training on risks; SDSs are used	-

Table X7-4: RMMs used for the handling of borates by companies				
Substance	**Operation**	**RMMs used**	**Other practices**	**Exposure (duration, concentration)**
	• Loading/unloading, milling, packaging, maintenance			
Disodium tetraborate, anhydrous	Manufacture of pharmaceuticals (laboratory)	Closed systems; glove boxes, fume hoods and ventilation used; restricted areas for authorised workers only; PPE: depends on risk assessment, but safety gloves, respiratory protection, safety glasses, safety shoes and protective clothing may be used	Hazard signs used; separate storage of personal and work clothing; training on risk management measures	5 mins per day and <10 times per year
Disodium tetraborate, anhydrous	Packing, discharging, loading/unloading	RMMs as specified in SDS; workers are trained on the use of PPEs		0.722 mg/m^3
Source: Consultation with companies through questionnaires				

X7.5.2 Dodecyl compounds

REACH measures

Dodecyl compounds have been registered for a wide variety of uses. Phenol, dodecyl-, branched has the following PROC codes:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 4: Chemical production where opportunity for exposure arises;
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities; and
- PROC 15: Use as laboratory reagent

Risk management measures for these PROC codes involve closed systems (PROC 1-3) whilst for the other PROC codes, exposure could occur and the risk management measures would need to be followed.

The uses of phenol, dodecyl-sulfurized, carbonates, calcium salts from the REACH registration dossier are for the following PROC codes:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 4: Chemical production where opportunity for exposure arises;
- PROC 5: Mixing or blending in batch processes;
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities;
- PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing);
- PROC 15: Use as laboratory reagent; and
- PROC 20: Use of functional fluids in small devices.

PROCs 1,2 and 3 involve the use of closed systems with no/little exposure, which is the first requirement under the CAD and CMD after substitution. Exposure is possible for the other PROC codes, for example PROC 20 involves filling and emptying systems that contain functional fluids.

For zinc bis[bis(dodecylphenyl)] bis(dithiophosphate), the PROC codes for use by workers are PROC 1, PROC 2, PROC 3, PROC 4, PROC 5, PROC 7, PROC 8a, PROC 8b, PROC 9, PROC 10, PROC 11, PROC 13, PROC 15 and PROC 20. PROCs 4, 5, 7, 8a, 8b, 9, 10, 11, 13, 15 and 20 would likely involve the potential of exposure, so risk management measures would be required.

Phenol, dodecyl-, sulfurized, carbonates, calcium salts is only pre-registered under REACH, so no risk management measures are available from REACH.

Phenol, dodecyl-, branched and Phenol, dodecyl-, sulfurized, carbonates, calcium salts as well as being classified as Repro 1B, are also classified as a Skin Corr. 1C (H314) and Eye Dam. 1 (H318) so the recommended risk management measures would also need to take these into account , i.e. skin and eye protection.

The recommended risk management measures from the REACH registration dossier for the dodecyl substances are discussed in the following table.

Table X7-5: Recommended RMMs for dodecyl substances from REACH registrations

Substance	Measure	Details
Phenol, dodecyl-branched	Organisational measures	PPE to be determined by a qualified person
	Engineering measures	Sufficient ventilation to remove and prevent build-up of vapours, dusts or fumes that could be generated during handling or thermal processing

Table X7-5: Recommended RMMs for dodecyl substances from REACH registrations		
Substance	**Measure**	**Details**
	Respiratory protection	Respirators as per a health and safety professional (OSHA (29 CFR 1910.133), ANSI (Z88.2-1992) or EN166 (Europe)); Maintain vapours, fumes or particulate levels below levels of concern (10 mg/m^3)
	Eye protection	Face shield for splash hazards; Safety glasses with side shields; Chemical goggles if splashing is possible Eye protection as per a health and safety professional (OSHA (29 CFR 1910.133) or EN166 (Europe))
	Skin and body protection	Appropriate hand protection; impervious gloves for prolonged contact
Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased	Organisational measures	-
	Engineering measures	Use in a well ventilated area
	Respiratory protection	Not normally required; Where oil mist is generated and the occupational exposure limit for oil must is exceeded, then an approved respirator with adequate protection is required; For using air-purifying respirators, use a particulate cartridge
	Eye protection	Special eye protection is normally not required; Safety glasses with side shields is good practice if splashing is possible
	Skin and body protection	Gloves (nitrile rubber, silver shield, or viton is recommended)
Phenol, dodecyl-, sulfurized, calcium salts	Organisational measures	-
	Engineering measures	Use in a well ventilated area
	Respiratory protection	Not normally required; Where oil mist is generated and the occupational exposure limit for oil must is exceeded, then an approved respirator with adequate protection is required; For using air-purifying respirators, use a particulate cartridge
	Eye protection	Special eye protection is normally not required; Safety glasses with side shields is good practice if splashing is possible
Phenol, dodecyl-, branched, sulfurized	Organisational measures	Handle in accordance with good industrial hygiene and safety practice
	Respiratory protection	For ordinary conditions of use- adequate ventilation Respirator with an approved filter in the case of vapour formation
	Eye protection	Tightly fitted safety goggles
	Skin and body protection	Use polyvinyl alcohol or butyl-rubber gloves; wash gloves with soap and water before removing; Use heat resistant gloves when handling hot material; Impervious clothing and choose according to the amount and concentration of the substance; Long sleeved clothing

Table X7-5: Recommended RMMs for dodecyl substances from REACH registrations		
Substance	**Measure**	**Details**
	Other	Do not eat or drink; do not smoke when using the substance; wash hands before breaks and at the end of the work day
Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate)	Organisational measures	Use the substance in a well ventilated area. Appropriate PPE is required if the engineering controls or work practices are insufficient for preventing contact.
Sources: ECHA (2018): Phenol, dodecyl-, branched REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14705/9 ECHA (2018): Phenol, dodecyl-, sulfurized, calcium salts, overbased REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15042/9 ECHA (2018): Phenol, dodecyl-, sulfurized, calcium salts REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/13858/9 ECHA (2018): Phenol, dodecyl-, branched, sulfurized REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/13858/9 ECHA (2018); Zinc bis{bis(dodecylphenyl)] bis (dithiophosphate) REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/12713/9		

Safety data sheets

Additional risk management measures are discussed in the safety data sheet for phenol, dodecyl-, branched. For engineering measures, it is recommended that measures such as process enclosures, process isolation, the introduction of equipment or process changes for minimising releases or contact, and the use of ventilation systems should be used.[256]

X7.5.3 Lead

REACH measures

Risk management measures for lead and lead compounds (lead di(acetate) and trilead dioxide phosphonate) from REACH registration dossiers are summarised below. Closed systems, organisational measures, respiratory protection, eye protection and skin and body protection are discussed.

The PROC codes for Lead registered under REACH are as follows:

- PROC 0: Other;
- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 4: Chemical production where opportunity for exposure arises;
- PROC 5: Mixing or blending in batch processes;
- PROC 7: Industrial spraying;
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities;

[256] Acros Organics (2017): Dodecylphenol Safety Data Sheet. Available at: https://www.fishersci.co.uk/chemicalProductData_uk/wercs?itemCode=10569282&lang=EN

- PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing);
- PROC 15: Use as laboratory reagent;
- PROC 22: Potentially closed processing operations with minerals/metals at elevated temperature. Industrial setting;
- PROC 25: Other hot work operations with metals; and
- PROC 26: Handling of solid inorganic substances at ambient temperature.

For PROCs 1 and 3, this involves closed systems (which is the first requirement under the CAD and CMD after substitution) so exposure will be to a minimum. For the other PROC codes, other risk management measures would be needed as specified in the guidance for safe use in the REACH registration dossier.

The PROC codes that are relevant for trilead dioxide phosphonate are:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 4: Chemical production where opportunity for exposure arises;
- PROC 5: Mixing or blending in batch processes;
- PROC 6: Calendering operations;
- PROC 7: Industrial spraying;
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities;
- PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing);
- PROC 10: Roller application or brushing ;
- PROC 14: Tabletting, compression, extrusion, pelletisation, granulation;
- PROC 21: Low energy manipulation of substances bound in materials and/or articles;
- PROC 22: Potentially closed processing operations with minerals/metals at elevated temperature. Industrial setting; and
- PROC 24: High (mechanical) energy work-up of substances bound in materials and/or articles.

PROC 1, 2, 3 involve the use of closed systems (under the CAD and CMD this is the first option after substitution); whilst the other processes would involve the use of additional risk management measures, for example the use of LEV, respiratory protection and PPE.

Table X7-6: Recommended RMMs for lead substances from REACH registration information		
Substance	**Measure**	**Details**
Lead	Organisational measures	General protective and hygienic measures Requirements for storage rooms and vessels
	Respiratory protection	Use of suitable respiratory protection is recommended; For brief exposure, a dust mask or half mask with particle filter P2 is recommended;
	Eye protection	Safety glasses
	Skin and body protection	Protective gloves (neoprene or leather)
	Handling	Provide good ventilation of the working area
Lead di(acetate)	Organisational measures	Obtain special instructions before use; avoid exposure; keep working clothes separately; take off all contaminated clothing immediately
	Respiratory protection	Full mask
	Eye protection	Safety glasses
	Skin and body protection	Natural latex gloves (break through time of >480 min and a glove thickness of 0.6 mm – EN 374 standard) Protective suit (EN 340, 463, 468, 943-1, 943-2); safety shoes (EN-ISO 20345)
	Other	PPE must be in accordance with EN 136, 140 and 149
Trilead dioxide phosphonate	Organisational measures	During work: do not eat, drink, smoke or sniff; shower or bath at the end of work; keep away from foodstuffs, beverages and feed; immediately remove all contaminated clothing; wash hands before breaks and at the end of work
	Respiratory protection	A suitable respiratory protection device is recommended; for brief exposure or low pollution use a dust mask or a half mask with particle filter P2
	Eye protection	Safety glasses
	Skin and body protection	Use protective gloves (neoprene or leather) Protective work clothing
Source: ECHA (2018): Lead REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/16063/9 ECHA (2018): Lead di(acetate) REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/13113/9 ECHA (2018): Trilead dioxide phosphonate REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/16140/9		

Safety Data Sheets

In addition, the safety data sheet for lead recommends the use of a full face particle respirator type P3 (EN 143) respiratory cartridges if this is needed; the safety gloves must satisfy European Directive 89/686/EEC and have the EN 374 standard; and also complete suit protection.[257]

[257] Sigma Aldrich (2017): Lead Safety Data Sheet. Available at: https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=391352&brand=ALDRICH&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2F391352%3Flang%3Den

International Lead Association guidance

The International Lead Association (ILA) has produced a number of guidance notes for reducing occupational exposure to lead.[258] General risk management measures that are recommended are:[259]

- Engineering and ventilation controls: The enclosure of equipment, negative draft exhaust systems (extract dust back into enclosures), and/or the use of specific LEV, should be installed where there are unavoidable emission sources. Work area ventilation should be balanced and air captured by the ventilation system may require treatment before discharge or recirculation;
- Workplace cleaning: Frequent washing/HEPA vacuuming is essential and the workplace should be cleaned after every shift;
- Personal Protective Equipment: A compliance policy should be considered where an assessment has indicated that PPE is needed, clean work clothes should be provided daily to workers in areas of significant exposure with the work clothing cleaned on-site by the employer under controlled conditions. Respirator and mask fit testing, cleaning and filter change regimes should also be maintained and workers should ensure the safety equipment fits well, is in good condition and the instructions for use are followed;
- Personal hygiene: Employers should ensure that workers have knowledge of basic, essential hygiene rules and these should be enforced. This includes workers in high exposure areas at the end of their shift passing through a room with wash basins to wash hands, then a 'plant side' changing room for removing work clothing, then through showers on the 'clean' side for changing into personal clothes; and
- Blood lead monitoring: A blood lead monitoring program should be put in place.

Specific measures are recommended for emissions.[260] Releases of lead (which would thus result in exposure) can occur during crushing operations (dust); sintering; transportation; furnace charging, smelting and tapping (lead smelting plants); battery breaking; and refining in primary and secondary circuits. The following measures are recommended for reducing exposure:

- The use of LEV and clean air stations with positive filtered air;
- Vehicles with enclosed cabs that have positive-pressure HEPA filtered air;
- Respiratory protection for those workers involved in processing operations;
- Regularly wash down areas with water and also keep working surfaces damp;
- Never dry sweep process areas; and
- Contain the whole process in one enclosed building if possible and separate operations from each other.

The ILA has also issued guidance notes on the design of changing room and washing facilities and effluent control and monitoring.[261]

[258] International Lead Association (2018): Guidance Notes. Available at: https://www.ila-lead.org/responsibility/guidance-notes

[259] International Lead Association (undated): General Information for Managers and Workers. Available at: https://www.ila-lead.org/UserFiles/File/guidancenotes/ILA_GN_General_V04.pdf

[260] International Lead Association (undated): Control and Monitoring of Atmospheric Emissions. Available at: https://www.ila-lead.org/UserFiles/File/guidancenotes/ILA9149_GN_Atmospheric_V04b.pdf

[261] (a) International Lead Association (undated): Design of Changing Rooms and Washing Facilities. Available at: https://www.ila-lead.org/UserFiles/ILA_GN_Changing_V05.pdf and (b) International Lead Association (undated): Effluent Control and Monitoring. Available at: https://www.ila-lead.org/UserFiles/File/guidancenotes/ILA_GN_Effluent_V04.pdf

Table X7-7: Control of emissions	
Process	**Risk Management Measures**
Furnace operations	Enclose furnace operations
Reaction temperatures	Reduce, where possible kettle or crucible temperatures for decreasing the rate of dross formation and the generation of sulphur dust
Furnace metal	Tap into moulds/pots under a ventilated shroud or directly into a bath with covered and ventilated lead for minimising fugitive emissions
Layout of the plant	The plant layout can be modified to reduce the quantity of materials handled and transported from one process to the next process
Ingot casting	Reduce temperature to below 500 ^{o}C for reducing emissions with a controlled flow rate to reduce dross formation
Mechanical operations	Where possible, for tasks with high exposure use mechanical means
Capturing emissions	Capture dust or fumes; isolate emission sources using LEV or an appropriate sized baghouse filter plant
Exhaust characteristics	The capture velocity of the exhaust hood needs to be great enough to prevent dust or fumes from escaping from the air flow; Face velocity required will be at a minimum, one metre per second
Process risk assessment	Perform a risk assessment of the process; establish safe procedures; establish monitoring, inspection and maintenance regimes where engineering controls are used
Source: International Lead Association (undated): Control and Monitoring of Atmospheric Emissions. Available at: https://www.ila-lead.org/UserFiles/File/guidancenotes/ILA9149_GN_Atmospheric_V04b.pdf	

Consultation responses

Risk management measures that are in place in companies for reducing workplace exposure to lead are set out in the following table. Generally, these measures are the same as those recommended by the International Lead Association (such as separate lockers and restricting access).

Table X7-8: RMMs used for the handling of lead by companies				
Substance	**Operation**	**RMMs used**	**Other practices**	**Exposure (duration, concentration)**
Lead	Electroplating; metallisation; soldering; production line operators; maintenance workers	Restricted areas; PPE classified by the work place and EN standard	No eating, drinking and smoking at the work site; separate storage of work and personal clothing; workers complete chemicals safe handling course	7.5 hours a day for production operators; 1 hour a day for maintenance workers Lead exposure level varies between 0.0016 mg/m^3-0.006 mg/m^3
Lead	Plate manufacturing; assembly operations; batteries; shipments and logistics	Risk assessments carried out; respiratory protection; gloves provided; training programs	Smoke free areas; each worker has two lockers (one for work clothes and one for street clothes); and vestibules for	7.5 hours per day: air concentration of Pb: <10-<100 µg/Nm^3)[262]

[262] Normal cubic meter; unspecified pressure, and temperature

Table X7-8: RMMs used for the handling of lead by companies				
Substance	**Operation**	**RMMs used**	**Other practices**	**Exposure (duration, concentration)**
			washing and storage;	
Lead di(acetate)	Manufacture of pharmaceuticals (QC testing)	PPE is used; laboratory areas are designed to minimise risk (such as air changes); dangerous chemicals are locked	No eating, drinking and smoking; separate storage of work and personal clothing; and washing facilities provided	1 hour per week of exposure
Lead di(acetate)	Manufacture of pharmaceuticals (laboratory uses)	Closed systems; glove boxes, fume hoods and ventilation used; restricted areas for authorised workers only; PPE: depends on risk assessment, but safety gloves, respiratory protection, safety glasses, safety shoes and protective clothing may be used	Hazard signs used; separate storage of personal and work clothing; training on risk management measures	5 mins per day and <10 times per year
Source: Consultation with companies through questionnaires				

X7.5.4 Retinol

REACH measures

Both retinol and retinyl palmitate have the same recommended risk management measures. These are organisational measures; the use of respiratory protection in the case of vapour/particle release; use of safety glasses and gloves and also the use of a chemical protection suit and boots if required. Retinol is also classified as a Skin Sens. 1 (H317) and an Eye Irrit. 2 (H319).

No PROC codes are listed in the registration dossier for retinol. The PROC codes listed for uses at industrial sites for retinyl palmitate are:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 4: Chemical production where opportunity for exposure arises;
- PROC 5: Mixing or blending in batch processes;
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities;

- PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing);
- PROC 14: Tabletting, compression, extrusion, pelletisation, granulation; and
- PROC 15: Use as a laboratory reagent

The use of retinyl palmitate in a number of these PROC codes would involve exposure; so risk management measures would need to be adopted as per the recommended measures in the dossier (PROCs 1-3 involve the use of closed system with little/no exposure).

Table X7-9: Recommended RMMs for retinol substances from REACH registrations

Substance	Measure	Details
Retinol	Organisational measures	Handle in accordance with good hygiene and safety practice; the product must not come into contact with the skin pregnant women and must also not be inhaled
	Respiratory protection	Respiratory protection in case of vapour/aerosol release; a particle filter with medium efficiency is required for liquid and solid particles (EN 143 or EN 149, Type P2 or FFP2)
	Eye protection	Safety glasses with side shields such as EN 166
	Hand protection	Chemical resistant gloves (EN 374, protective index 6 recommended > 480 minutes of permeation) such as nitrile rubber (0.4 mm), chloroprene rubber (0.5 mm) and butyl rubber (0.7 mm)
	Skin and body protection	Chosen depending on the activity such as aprons, chemical protection suit and protecting boots (for splashes according to EN 14605 or for dust, EN ISO 13982)
Retinyl palmitate	Organisational measures	Handle in accordance with good hygiene and safety practice; the product must not come into contact with the skin pregnant women and must also not be inhaled
	Respiratory protection	Respiratory protection in case of vapour/aerosol release; a particle filter with medium efficiency is required for liquid and solid particles (EN 143 or EN 149, Type P2 or FFP2)
	Eye protection	Safety glasses with side shields such as EN 166
	Hand protection	Chemical resistant gloves (EN 374, protective index 6 recommended > 480 minutes of permeation) such as nitrile rubber (0.4 mm), chloroprene rubber (0.5 mm) and butyl rubber (0.7 mm)
	Skin and body protection	Chosen depending on the activity such as aprons, chemical protection suit and protecting boots (for splashes according to EN 14605 or for dust, EN ISO 13982)

Sources: ECHA (2018): Retinol REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/11075/9
ECHA (2018): Retinol palmitate REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/13687/9

Safety Data Sheets

Additional measures for retinol that is included in its safety data sheet concerns respiratory protection. The safety data sheet advises that for higher level of respiratory protection, the use of type ABEK-P2 respiratory cartridges is recommended.[263]

X7.5.5 Organotins

REACH measures

Dibutyltin dilaurate is used in industrial setting/by professional workers in the following PROC codes:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 4: Chemical production where opportunity for exposure arises;
- PROC 5: Mixing or blending in batch processes;
- PROC 6: Calendering operations;
- PROC 7: Industrial spraying;
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities;
- PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing);
- PROC 10: Roller application or brushing;
- PROC 11: Non-industrial spraying;
- PROC 13: Treatment of articles by dipping and pouring;
- PROC 14: Tabletting, compression, extrusion, pelletisation, granulation;
- PROC 15: Use as a laboratory reagent;
- PROC 19: Manual activities involving hand contact;
- PROC 21: Low energy manipulation and handling of substances bound in/or materials or articles; and
- PROC 24: High (mechanical) energy work-up of substances bound in/or materials or articles

A wide number of these PROC codes would involve exposure to dibutyltin laurate and the recommended risk management measures would need to be followed to minimise exposure. Dibutyltin dichloride is used in closed processes (PROCs 1 and 3); however, the substance is also used where exposure could occur (PROCs 4, 5, 8b, 9, 14 and 15). The PROC codes for the use of dibutyltin oxide are similar of those for dibutyltin laurate. For example, exposure could occur for PROCs 4, 5, 6, 7, 8a, 8b, 9, 10, 11, 13 and 14.

[263] Sigma Aldrich (2017): Retinol Safety Data Sheet. Available at: https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=R7632&brand=SIGMA&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Fsigma%2Fr7632%3Flang%3Den

2-ethylhexyl 10-ethyl-4,4-dicotyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate is used in the following processes:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 6: Calendering operations;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities;
- PROC 14: Tabletting, compression, extrusion, pelletisation, granulation; and
- PROC 21: Low energy manipulation and handling of substances bound in/or materials

The risk management measures recommended for tin compounds in the REACH registration dossiers are set out below. For a number of tin compounds, the recommended RMMs are the same. In the case of 2-ethylhexyl 10-ethyl-4,4-dicotyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate, RMMs for use with machinery is also discussed (as per its PROCs code listed previously). Dibutyltin oxide is classified as a Skin Sens.1 (H317), Skin Irrir.2 (H315) and also Eye Dam. 1 (H318) alongside its Repro. 1B classification. Dibutyltin bis (2-ethylhexanoate) is classified as a STOT RE1 (H372) with some notifiers also including additional classifications for Skin Corr. 1B (H314) and Skin Sens. 1 (H317).

Table X7-10: Recommended RMMs for tin substances from REACH registrations

Substance	Measure	Details
Dibutyltin dilaurate; dibutyltin dichloride; Dibutyltin bis (2-ethylhexanoate)	Organisational measures	Do not eat or drink at work; immediately remove contaminated clothing
	Respiratory protection	Gas filter type A if the occupational exposure limit or MAK value will be exceeded
	Eye protection	Safety glasses
	Skin and body protection	Chemical resistant protective clothing
	Hand protection	PVC or rubber protective gloves
Dibutyltin oxide	Organisational measures	Do not eat or drink at work; immediately remove contaminated clothing
	Respiratory protection	Particle filter FFP1 if the occupational exposure value or MAK value will be exceeded
	Eye protection	Safety glasses
	Skin and body protection	Chemical resistant protective clothing
	Hand protection	PVC or rubber protective gloves
2-ethylhexyl 10-ethyl-4,4-dicotyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate	Organisational measures	Appropriate exhaust ventilation at machinery; frequently monitor and control the working atmosphere
	Respiratory protection	Wear suitable respiratory equipment in case of hazardous fumes
	Eye protection	Safety glasses
	Hand protection	PVC or neoprene gloves
Sources: ECHA (2018): Dibutyltin dilaurate REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14904/9 ECHA (2018): Dibutyltin dichloride REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14904/9 ECHA (2018): Dibutyltin oxide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14790/9		

ECHA (2018): 2-ethylhexyl 10-ethyl-4,4-dicotyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14171/9

Safety Data Sheets

Additional risk management measures are recommended in the safety data sheets for the tin compounds. For example, in the safety data sheet for dibutyltin dilaurate provided by suppliers, use of a full-face respirator and a face shield is also listed.[264] In the safety data sheet for dibutyltin oxide, one supplier also recommends the use of a full-face particle respirator type P3 (EN 143) if the risk assessment shows respiratory protection is required.[265]

Consultation responses

Identified risk management measures for dibutyltin dilaurate are the following from consultation:

- Risk assessments are undertaken for all processes;
- Closed processes are used for transferring substances;
- Dosing of solvents is performed automatically via pipes;
- LEV (Local Exhaust Ventilation) is used in filling lines and some automatization in the filling lines;
- Safety cards are used for the substance PPE to be used;
- No eating, drinking or smoking in use areas;
- Restricted access to laboratories and production areas;
- Separate storage of work and personal clothing;
- Training of new staff and production workers alongside a safety campaign.

Exposure to the substance is from less than one hour a day (for example, laboratory processes) to four hours a day (loading operations).

X7.5.6 4,4'-isopropylidenediphenol (Bisphenol A, BPA)

REACH measures

BPA under REACH is registered as being used in the following processes (PROC codes):

- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 4: Chemical production where opportunity for exposure arises;

[264] Sigma Aldrich (2017): Dibutyltin dilaurate Safety Data Sheet. Available at: https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=291234&brand=ALDRICH&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fsearch%3Fterm%3DDibutyltin%2Bdilaurate%26interface%3DAll%26N%3D0%26mode%3Dmatch%2520partialmax%26lang%3Den%26region%3DGB%26focus%3Dproduct

[265] Sigma Aldrich (2017): Dibutyltin (IV) oxide Safety Data Sheet. Available at: https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=183083&brand=ALDRICH&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fsearch%3Fterm%3Ddibutyltin%2Boxide%26interface%3DAll%26N%3D0%26mode%3Dmatch%2520partialmax%26lang%3Den%26region%3DGB%26focus%3Dproduct

- PROC 5: Mixing or blending in batch processes;
- PROC 6: Calendering operations;
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities;
- PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing);
- PROC 10: Roller application or brushing;
- PROC 11: Non industrial spraying;
- PROC 12: Use of blowing agents in manufacture of foam;
- PROC 13: Treatment of articles by dipping and pouring;
- PROC 14: Tabletting, compression, extrusion, pelletisation, granulation; and
- PROC 21: Low energy manipulation of substances bound in materials and/or articles

For PROCs 2 and 3, this involves closed systems (which is the first requirement under the CAD and CMD after substitution) so exposure will be reduced to a minimum. Other risk management measures that are recommended are discussed in the table below. BPA is also classified as a skin sensitiser (H317), STOT SE 3 (H317) and also Eye Damage (H318).

Table X7-11: 4,4-isoproylidenediphenol risk management measures	
Measure	**Details**
Ventilation	LEV is required for sample and charging/discharging activities
Organisational measures	Procedural and/or control techniques to minimise exposure during cleaning and maintenance and where the OEL may be exceeded
Respiratory protection	Half mask with a FFP2 particle filter (DIN EN 149) in the presence of dust
Eye protection	Eye/face protection is required; Chemical googles (EN 166 or equivalent)
Hand protection	Permeation resistant gloves with suitable materials: Laminate gloves of Polyethylene and ethylene/vinyl alcohol copolymer; Nitrile rubber with a thickness of >=0.35 mm The disposal of gloves after contamination is recommended
Skin and body protection	Suitable protective clothing is required
Handling	Ensure adequate ventilation; if necessary use exhaust ventilation; Avoid contact with eye, skin and inhalation of dust and vapour
Source: ECHA (2018): 4,4'-isopropylidenediphenol REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15752/9	

Safety Data Sheets

The SDS supplied to downstream users, recommends that where the risk assessment shows that air-purifying respirators are appropriate to use a full-face particle respirator type P3 (EN 143) respirator cartridges for backup to engineering controls.[266]

[266] Sigma Aldrich (2017): Bisphenol A Safety Data Sheet. Available at: https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=239658&brand=ALDRICH&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fsearch%3Fterm%3Dbisphenol%2BA%26interface%3DAll%26N%3D0%26mode%3Dmatch%2520partialmax%26lang%3Den%26region%3DGB%26focus%3Dproduct

Consultation responses

Identified risk management measures for BPA are the following from consultation:

- Risk assessments are undertaken for all processes;
- Closed process for transferring
- Dosing of solvents is performed automatically via pipes;
- LEV (Local Exhaust Ventilation) is used in filling lines and some automatization in the filling lines;
- Safety cards are used for the substance to identify PPE to be used;
- No eating, drinking or smoking;
- Restricted access to laboratories and production areas;
- Separate storage of work and personal clothing;
- Training of new staff and production workers alongside a safety campaign.

Exposure to the substance is from less than one hour a day (for example laboratory processes) to four hours a day (loading operations).

X7.5.7 Dinoseb

REACH measures

The RMMs listed in the REACH Registration dossiers for reducing exposure are discussed in the following table. Dinoseb is also classified as an Eye Irrit. 2 (H319) so eye protection will be necessary.

Dinoseb is listed as being used for the following PROC codes:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 4: Chemical production where opportunity for exposure arises; and
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities.

Exposure controls would be needed for PROC 2, 4 and 8b.

Table X7-12: Dinoseb REACH protective measures	
Measure	**Details**
Organisational measures	Do not eat or drink at work; immediately remove contaminated clothing
Engineering measures	Ensure there is sufficient ventilation; storage room floor must be impermeable to prevent the escape of liquids
Respiratory protection	For emergencies: use self-contained breathing apparatus; Particle filter size P1 (EN143)
Eye protection	Safety glasses with side shields
Hand protection	Compatible chemical resistant gloves
Skin and body protection	Protective clothing
Source: ECHA (2018): Dinoseb REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/12446/9	

Safety Data Sheets

The safety data sheet provided to the consultants for dinoseb additionally recommends the following measures:[267]

- Eye/face protection: Use face shield and safety glasses that meet NIOSH (US) or EN 166 (EU) standards;
- Skin protection: For full protection use chloroprene gloves and for splash contact use natural latex/chloroprene;
- Body protection: Use complete suit protection; and
- Respiratory protection: Where the risk assessment shows respiratory protection is required, then a full face respirator type N100 (US) with type P3 (EN 143) respiratory cartridges as back up to engineering controls. If no engineering controls are used, then a full face respirator is recommended.

X7.5.8 Imidazolidine-2-thione

REACH measures

Imidazolidine-2-thione is listed as being used in the following PROC codes:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 4: Chemical production where opportunity for exposure arises;
- PROC 5: Mixing or blending in batch processes;
- PROC 7: Industrial spraying;
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities;
- PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing);
- PROC 10: Roller application or brushing;
- PROC 13: Treatment of articles by dipping and pouring;
- PROC 14: Tabletting, compression, extrusion, pelletisation, granulation;
- PROC 15: Use as a laboratory reagent;
- PROC 21: Low energy manipulation of substances bound in materials and/or articles; and
- PROC 24: High (mechanical) energy work-up of substances bound in/or materials or articles

In terms of exposure, these PROC codes would involve possible exposure so protective measures would need to be followed (although PROC 1 and 3 are use closed systems).

[267] Sigma Aldrich (2017): Dinoseb Safety Data Sheet. Available at: https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=442570&brand=SUPELCO&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Fsupelco%2F442570%3Flang%3Den

The RMMs listed in the REACH registration dossier are described below, and include organisational measures, respiratory protective, eye protection, hand protection and skin and body protection listed for reducing exposure.

Table X7-13: Imidazolidine-2-thione REACH protective measures	
Measure	**Details**
Organisational measures	Maintain strict body hygiene; avoid contact with skin, eyes and dust inhalation
Engineering measures	None listed
Respiratory protection	Dust mask
Eye protection	Safety glasses
Hand protection	Gloves
Skin and body protection	Protective clothing
Source: ECHA (2018): Imidazolidine-2-thione REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/13536/9	

Safety data sheets

The safety data sheet supplied to downstream users recommends that where the risk assessment shows that air-purifying respirators are appropriate to use a full-face particle respirator with type P3 (EN 143) respirator cartridges for backup to engineering controls. If the respiratory is the only mean of protection, then the use of a full-face supplied air respirator is recommended.[268]

X7.5.9 4-tert-butylbenzoic acid

REACH measures

The substance is used at industrial sites for the following:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 6: Calendering operations;
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities;
- PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing);
- PROC 14: Tabletting, compression, extrusion, pelletisation, granulation;
- PROC 15: Use as a laboratory reagent; and
- PROC 21: Low energy manipulation of substances bound in materials and/or articles;

[268] Sigma Aldrich (2014): 2-Imidazolidinethione Safety Data Sheet. Available at: https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=I504&brand=ALDRICH&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fsearch%3Fterm%3D2-Imidazolidinethione%26interface%3DAll%26N%3D0%26mode%3Dmatch%2520partialmax%26lang%3Den%26region%3DGB%26focus%3Dproduct

In terms of exposure, PROCs 6-15 would involve exposure potential so RMM (such as those listed) would need to be followed. PROCs 3 and 21 have the potential for exposure.

The risk reduction measures discussed in REACH for exposure control for 4-tert-butylbenzoic acid are described in the following table.

Table X7-14: 4-tert-butylbenzoic acid REACH protective measures	
Measure	**Details**
Organisational measures	Keep away from foodstuffs, beverages and feed; avoid contact with skin; wash hands before breaks and at the end of work; vacuum clean contaminated clothing; remove soiled and contaminated clothing immediately; ensure washing facilities are available at the workplace; provide an eye bath
Engineering measures	Ensure good ventilation/exhaustion at the workplace
Respiratory protection	Use a respiratory filter device for brief exposure or low pollution; Use a respiratory protective device which is independent of circulating air for longer or intensive exposure; Short term filter device: P3 filter; Only use breathing equipment for handling the residual risk were all other risk minimising measures have been carried out, such as local exhaust and/or retention
Eye protection	Goggles recommended during refilling
Hand protection	Chemical resistant gloves; apply skin-cleaning agents and skin cosmetics after use of gloves; for using undissolved solid substance nitrile rubber (NBR), butyl rubber (BR), Polychloroprene rubber (CR) or fluorocarbon rubber (FKM) may be suitable
Skin and body protection	Protective clothing (apron, boots)
Source: ECHA (2018): 4-tert-butylbenzoic acid REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/12153/9	

Safety Data Sheets

The safety data sheet for 4-tert-buylbenzoic acid recommends the following measures:[269]

- Eye/face protection: Use face shield and safety glasses that meet NIOSH (US) or EN 166 (EU) standards;
- Skin protection: Use nitrile rubber gloves for full contact and splash contact;
- Body protection: Use complete suit protection; and
- Respiratory protection: Where the risk assessment shows respiratory protection is required, then a full face respirator type N99 (US) or type P2 (EN 143) respiratory cartridges as back up to engineering controls. If no engineering controls are used, then a full face respirator is recommended; and
- Provide appropriate ventilation where dust can occur.

[269] Sigma Aldrich (2017): 4-tert-butylbenzoic acid Safety Data Sheet. Available at: https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=150355&brand=ALDRICH&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2F150355%3Flang%3Den

X7.5.10 2-ethoxyethanol

REACH measures

The substance is used in the following PROC codes, with exposure potential for PROCs 3-15, so protective measures may be needed (as listed above) to reduce exposure:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 5: Mixing or blending in batch processes;
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities;
- PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing); and
- PROC 15: Use as a laboratory reagent.

The RMMs identified for 2-ethoxyethanol involve hygiene measures, respiratory protection, eye protection, hand protection and skin and body protection. These recommended measures are described in the following table.

Table X7-15: 2-ethoxyethanol REACH protective measures

Measure	Details
Organisational measures	Only use under strictly controlled conditions; keep away from foodstuffs, beverages and feed; do not eat, drink, smoke or sniff whilst working; wash hands before breaks and at the end of work; immediately remove soiled, soaked clothing and use again only after washing; store protective clothing separately; avoid contact with eyes and skin
Engineering measures	None listed
Respiratory protection	Use a respiratory filter device for brief exposure or low pollution; Use a respiratory protective device which is independent of circulating air for longer or intensive exposure; Short term filter device: Filter A; Only use breathing equipment for handling the residual risk where all other risk minimising measures have been carried out, such as local exhaust and/or retention
Eye protection	Tightly sealed goggles
Hand protection	Solvent resistant gloves; apply skin-cleaning agents and skin cosmetics after use of gloves The following materials are not suitable: Polychloroprene rubber (CR), nitrile rubber (NBR), Natural rubber (NR) and fluorocarbon rubber (FKM)
Skin and body protection	Flame retarding, antistatic protective clothing. Solvent resistant protective clothing
Source: ECHA (2018): 2-ethoxyethanol REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14915/9	

Safety Data Sheets

The safety data sheet for 2-ethoxyethanolrecommends the following measures:[270]

- Eye/face protection: Use face shield and safety glasses that meet NIOSH (US) or EN 166 (EU) standards;
- Skin protection: Use butyl rubber gloves for full contact and nitrile rubber gloves for splash contact;
- Body protection: Use complete suit protection and flame retardant antistatic protective clothing when needed; and
- Respiratory protection: Where the risk assessment shows respiratory protection is required, then a full face respirator type N99 (US) or type P2 (EN 143) respiratory cartridges as back up to engineering controls. If no engineering controls are used, then a full face respirator is recommended.

X7.5.11 DMF: N,N-Dimethyl Formamide[271]

REACH measures

The substance is used in the following PROC codes, with exposure potential for PROCs 3-19, so protective measures may be needed (as listed below) to reduce exposure:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 4: Chemical production where opportunity for exposure arises
- PROC 5: Mixing or blending in batch processes
- PROC 7: Industrial spraying
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities;
- PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing);
- PROC 10: Roller application or brushing
- PROC 14: Tabletting, compression, extrusion, pelletisation, granulation
- PROC 15: Use as a laboratory reagent.
- PROC 19: Hand-mixing with intimate contact and only PPE available

[270] Sigma Aldrich (2017): 2-ethoxyethanol Safety Data Sheet. Available at: https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=128082&brand=SIGALD&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fsearch%3Fterm%3D2-ethoxyethanol%26interface%3DAll%26N%3D0%26mode%3Dmatch%2520partialmax%26lang%3Den%26region%3DGB%26focus%3Dproduct

[271] http://www.emdmillipore.com/Web-US-Site/en_CA/-/USD/ProcessMSDS-Start?PlainSKU=MDA_CHEM-100397&Origin=PDP accessed 24 November 2018

The RMMs identified for N,N-Dimethyl Formamide involve hygiene measures, respiratory protection, eye protection, hand protection and skin and body protection. These recommended measures are described in the following table.

Safety Data Sheets

The safety data sheet for N,N-Dimethyl Formamide commends the following measures:

- Eye/face protection: Use safety glasses;
- Skin protection: Use butyl rubber gloves for full contact and Viton (R) gloves for splash contact;
- Body protection: Use flame retardant antistatic protective clothing; and
- Respiratory protection: required when vapours/aerosols are generated; use recommended filter type Filter A- (P2).

Table X7-16: N,N-Dimethyl Formamide REACH protective measures	
Measure	**Details**
Organisational measures	Do not eat, drink or smoke when using this product; wash hands after handling; Remove contaminated clothing and protective equipment before entering eating areas.
Engineering measures	Ensure adequate ventilation, especially in confined areas
Respiratory protection	Wear respiratory protection if ventilation is inadequate. Gas filter for gases/vapours of organic compounds.
Eye protection	Tightly fitting safety goggles; Face-shield; Respirator with a full face mask
Hand protection	Use solvent-resistant gloves (butyl-rubber); Neoprene gloves • The selected protective gloves have to satisfy the specifications of EU Directive 89/689/EEC and the standard EN 374 derived from it • The suitability for a specific workplace should be discussed with the producers of the protective gloves
Skin and body protection	Wear suitable protective equipment • Complete suit protecting against chemicals • Take note of occupational restrictions for women of child bearing age
Source: ECHA (2018): N,N-Dimethyl Formamide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15093	

X7.5.12 NMP: 1-Methyl-2-Pyrrolidone[272]

REACH measures

The substance is used in the following PROC codes, with exposure potential for PROCs 3-21, so protective measures may be needed (as listed above) to reduce exposure:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions;

272 https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=328634&brand=SIAL&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Fsial%2F328634%3Flang%3Den accessed 24 November 2018

- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 4: Chemical production where opportunity for exposure arises
- PROC 5: Mixing or blending in batch processes;
- PROC 6: Calendering operations
- PROC 7: Industrial spraying
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities;
- PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing);
- PROC 10: Roller application or brushing
- PROC 13: Treatment of articles by dipping and pouring
- PROC 14: Tabletting, compression, extrusion, pelletisation, granulation
- PROC 15: Use as a laboratory reagent.
- PROC 17: Lubrication at high energy conditions in metal working operations
- PROC 18: General greasing / lubrication at high kinetic energy conditions
- PROC 21: Low energy manipulation of substances bound in materials and/or articles

The RMMs identified for 1-Methyl-2-Pyrrolidone involve hygiene measures, respiratory protection, eye protection, hand protection and skin and body protection. These recommended measures are described in the following table.

Table X7-17: 1-Methyl-2-Pyrrolidone REACH protective measures	
Measure	**Details**
Organisational measures	Avoid contact with the skin, eyes and clothing. Females in early pregnancy under no circumstances should come in contact (skin/inhalation) with the substance. Take off immediately all contaminated clothing. Wash contaminated clothing before reuse. Gloves must be inspected regularly and prior to each use.
Engineering measures	None listed
Respiratory protection	Respiratory protection required in case of exceeding the occupational exposure limit: Gas filter for gases/vapours of organic compounds Respiratory protection in case of vapour/aerosol release. Combination filter for gases/vapours of organic compounds and solid and liquid particles
Eye protection	Safety glasses with side-shields (frame goggles)
Hand protection	Use chemical resistant protective gloves; butyl rubber in case of prolonged, direct contact and nitrile rubber/chloroprene rubber for short term contact
Skin and body protection	Body protection must be chosen depending on activity and possible exposure
Source: ECHA (2018): 1-Methyl-2-Pyrrolidone REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15493	

Safety Data Sheets

The safety data sheet for 1-Methyl-2-Pyrrolidone commends the following measures:

- Eye/face protection: Use safety glasses with side-shields conforming to EN166. Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU).

- Skin protection: Use inspected gloves (satisfying the specifications of EU Directive 89/686/EEC and the standard EN 374). For Full contact, use butyl rubber gloves for full contact and Nature latex/chloroprene gloves for splash contact. If used in solution, or mixed with other substances, and under conditions which differ from EN 374, contact the supplier of the CE approved gloves. Post-use remove the gloves using proper glove removal technique (without touching glove's outer surface) to avoid skin contact with this product.

- Body protection: Use Impervious clothing (must be selected according to the concentration and amount of the dangerous substance) flame retardant antistatic protective clothing; and

- Respiratory protection: Where risk assessment shows air-purifying respirators are appropriate use (US) or type ABEK (EN14387) respirator cartridges as a backup to enginee protection, use a full-face supplied air respirator. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

X7.5.13 DMAC: N,N-Dimethylacetamide[273]

REACH measures

The substance is used in the following PROC codes, with exposure potential for PROCs 3-15, so protective measures may be needed (as listed above) to reduce exposure:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 4: Chemical production where opportunity for exposure arises
- PROC 5: Mixing or blending in batch processes;
- PROC 7: Industrial spraying
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities;
- PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing)
- PROC 10: Roller application or brushing
- PROC 13: Treatment of articles by dipping and pouring
- PROC 14: Tabletting, compression, extrusion, pelletisation, granulation
- PROC 15: Use as a laboratory reagent.

The RMMs identified for N,N-Dimethylacetamide involve hygiene measures, respiratory protection, eye protection, hand protection and skin and body protection. These recommended measures are described in the following table.

[273] https://ws.eastman.com/ProductCatalogApps/PageControllers/MSDSShow_PC.aspx accessed 24 November 2018

Table X7-18: N,N-dimethylacetamide REACH protective measures	
Measure	**Details**
Organisational measures	Avoid contact with the skin, eyes and clothing. Avoid inhalation of vapour. Handle in accordance with good industrial hygiene and safety practice. Take off immediately all contaminated clothing. Store work clothing separately.
Engineering measures	None listed
Respiratory protection	Wear respiratory protection if ventilation is inadequate. Gas filter for gases/vapours of organic compounds.
Eye protection	Safety glasses with side-shields (frame goggles).
Hand protection	Chemical resistant protective gloves (EN 374). Suitable materials also with prolonged, direct contact (Recommended: Protective index 6, corresponding > 480 minutes of permeation time according to EN 374): butyl rubber (butyl) - 0.7 mm coating thickness.
Skin and body protection	Body protection must be chosen depending on activity and possible exposure, e.g. apron, protecting boots, chemical-protection suit (according to EN 14605 in case of splashes or EN ISO 13982 in case of dust).
Source: ECHA (2018): N,N-dimethylacetamide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15266	

Safety Data Sheets

- Eye/face protection: Use eye safety glasses with side-shields and face-shield
- Skin protection: Use Rubber gloves/Neoprene gloves with standard break through time and strength.
- Body protection: Suit protecting against chemicals should be used.
- Respiratory protection: Use respiratory protection unless adequate local exhaust ventilation is provided or exposure assessment demonstrates that exposures are within recommended exposure guidelines. Organic vapour type (A) filter is to be used as respiration protection measure.
- As protective measure, eye flushing systems and safety showers are ensured to be located close to the working place.

X7.5.14 Other Repro 1A/1Bs

Risk management measures that have been discussed sofar in this section are for the substances prioritized in Sub-task 2.3. For other reproductive 1A/1B substances, the risk management measures will be similar to those presented in this section, for example use in closed systems; the use of ventilation; hand, face, body and eye protection; respiratory protection; and organisational measures.

Consultation has identified the RMMs presented in the table below for other reproductive 1A/1B substances. These include a few additional measures to those summarized for the prioritized chemicals including:

- Risk assessment should be performed
- Information and training;
- Hazard / safety signs should be used;
- Safety cards should be used to identify appropriate PPE.

Table X7-19: RMMs used for the handling of reprotoxic substances by companies				
Substance	**Operation**	**RMMs used**	**Other practices**	**Exposure (duration, concentration)**
Other	Assembly	LEV; control measures and equipment; suitable PPE; matrix system for PPE; risk assessments performed	Segregated areas for clothing; no eating, drinking and smoking in work areas	1 hour per week
Other (including bromadiolone, brodifacoum and flocoumafen	Insecticides and rodenticides production	Aspiration systems in place; signs; PPE; information and training	No eating, smoking and drinking; separate storage of work and street clothing; washing and toilet facilities	7.5 hours per day
Other (includes Lead (II) methanesulfonate; Nickel (II) chloride; and Cobalt sulfate)	Electroplating; metallisation; soldering; production line operators; maintenance workers	Restricted areas; PPE classified by the work place and EN standard	No eating, drinking and smoking at the work site; separate storage of work and personal clothing; workers complete chemicals safe handling course	7.5 hours a day for production operators; 1 hour a day for maintenance workers Lead exposure level varies between 0.0016 mg/m^3-0.006 mg/m^3
Brodifacoum; Bromadiolone; Clorofacinone; Difenacoum	Pesticides and other agrochemical products manufacturing	PPE matrix; continuous ventilation; chemical risk assessments performed	No eating and drinking in production areas; changing rooms; separate storage of work and street clothing; showers; training	-
Other	Fertilisers manufacturing	PPE; standard operating procedures; SDS; and labelling	-	-
Brodifacoum; Bromadiolone; Difenacoum	Pesticides and other agrochemical products manufacturing	Closed systems used; automated dosing systems used; ventilation; restriction to areas; and PPE	-	Exposure times kept to a minimum
Source: Consultation with companies through questionnaires				

Annex 8 Examples of Strategic and Voluntary Approaches

X8.1 Introduction

This annex provides an overview of:

- Strategic approaches to controlling occupational risks from reprotoxic substances; and
- Voluntary industry initiatives adopted to date to reduce exposure to reproductive toxicants (e.g. Product Stewardships) and Social Partners Agreements in the areas concerned.

Note that we have also interpreted strategic approaches as being actions led or taken mainly by Member States, although some of the broader industry initiatives could also be considered to form the basis of a strategic approach. In contrast, voluntary initiatives are industry based, but may or may not be linked to initiatives launched by NGOs or public authorities.

X8.2 Strategic approaches

X8.2.1 Overview

This section focuses primarily on measures related to better eliminating or controlling occupational exposure to reprotoxic chemicals. It discusses the development of international-level systematic approaches aimed at achieving risk assessment and high-quality risk management. These include common policy frameworks, surveillance and biomonitoring, industry engagement initiatives and research programmes. National-level initiatives are also considered, with discussion of best practice in Member States as well as some of the challenges that exist at workplace implementation level.

X8.2.2 International initiatives

Common policy frameworks and strategies

The Strategic Approach to International Chemicals Management (SAICM)

The Strategic Approach to International Chemicals Management (SAICM) was created in 2006 to provide a common policy framework to promote chemical safety around the world. It was developed by a multi-stakeholder and multi-sectoral Preparatory Committee and supports the achievement of goals agreed at the 2002 Johannesburg World Summit on Sustainable Development**.** SAICM's overall objective is the achievement of the sound management of chemicals throughout their life cycle so that by the year 2020, chemicals are produced and used in ways that minimise significant adverse impacts on the environment and human health.[274] It is important both because of its comprehensive scope in terms of its ambitious "2020 goal" for sound chemicals management, but also due to its multi-stakeholder and multi-sectoral character, and the fact that it has been formally endorsed by the governing bodies of key intergovernmental organisations. It should also be noted that the United Nations Environment Programme has also adopted a 2030 agenda.[275]

[274] SAICM (2018): SAICM Overview. Strategic Approach to International Chemicals Management (SAICM). Available at: http://www.saicm.org/About/SAICMOverview/tabid/5522/language/en-GB/Default.aspx

[275] See https://wedocs.unep.org/bitstream/handle/20.500.11822/9851/-The_United_Nations_Environment_Programme_and_the_2030_Agenda_Global_Action_for_People_and_the_Planet-2015EO_Brochure_WebV.pdf.pdf?sequence=3&isAllowed=y

Within the Global Plan of Action, priority is to be given to activities which include to:

"Ensure that, by 2020:

i. Chemicals or chemical uses that pose an unreasonable and otherwise unmanageable risk to human health and the environment based on a science-based risk assessment and taking into account the costs and benefits as well as the availability of safer substitutes and their efficacy are no longer produced or used for such uses;

ii. The risks from unintended releases of chemicals that pose an unreasonable and otherwise unmanageable risk to human health and the environment based on a science-based risk assessment and taking into account the costs and benefits are minimized;…"

The groups of chemicals that might be prioritised in relation to the above include: persistent, bioaccumulative and toxic substances (PBTs); very persistent and very bioaccumulative substances; chemicals that are carcinogens or mutagens or that adversely affect, inter alia, the reproductive, endocrine, immune or nervous systems; persistent organic pollutants (POPs); mercury and other chemicals of global concern; chemicals produced or used in high volumes; chemicals subject to wide dispersive uses; and other chemicals of concern at the national level.

Global priorities are set across a range of objectives, which include the development of plans for prioritisation of action in consultation with stakeholders, including vulnerable groups. Examples of measures to safeguard the health of women and children are the minimisation of chemical exposures before conception and through gestation, infancy, childhood and adolescence. Occupational health and safety for workers would be promoted through measures such as the establishment of national inspection systems and implementation of adequate occupational health and safety standards to minimise workplace hazards from chemicals; this includes carcinogens, mutagens and reproductive toxins. Within this work area, the aim is to prioritise assessments and studies concerning such chemicals which may pose an unreasonable or otherwise unmanageable risk for human health and the environment. Reporting on this initiative for 2011 to 2013[276] suggests that almost 70% of governmental signatories had adopted mechanisms to address CMR substances, and just under 70% had prioritised this group of substances for chemical risk reduction. Interestingly, in addition, around 60% reported the existence of legislation/permits with respect to lead-acid batteries as a specific waste stream. Also interesting is the number of respondents that highlighted the involvement of the health sector in communication with vulnerable groups.

More recently, as part of new work activities within the Global Plan of Action is a package of measures aimed at reducing hazardous substances, within the life-cycle of electrical and electronic products. This specifically includes an action to "7. Prioritise the reduction of exposure; eliminate or substitute hazardous substances of concern in e-products and their production processes; and promote procurement processes that include this objective." Again, the hazardous substances of concern for this initiative include "carcinogens or mutagens or that adversely affect, among other things, the reproductive, endocrine, immune or nervous systems".[277]

[276] SAICM (2014): Progress in Strategic Approach Implementation for 2011-2013. Strategic Approach to International Chemicals Management (SAICM). Available at: http://www.saicm.org/Portals/12/Documents/reporting/k1403579-eowg2-inf4-second-progress-report.pdf

[277] SAICM (2014): Annex II – Inclusion of new activities relating to the environmentally sound management of nanotechnologies and manufactured nanomaterials and hazardous substances within the life-cycle of electrical and electronic products in the Global Plan of Action of the Strategic Approach. Strategic Approach to International Chemicals Management (SAICM). Available at: http://www.saicm.org/Portals/12/documents/saicmtexts/ICCM3-Annex-II-EN.pdf

An independent evaluation[278] of SAICM, whilst acknowledging the Strategic Approach's achievements in enabling cooperation, coordination, trust and information sharing across all stakeholder groups, also identified weaknesses and gaps in the Strategic Approach; most notable is the under-capacity of the SAICM Secretariat to deliver on its mandated functions, resulting in poor information flow down to the national level. Further work is needed if the goal of reducing inequality within and between countries in relation to chemicals management is to be realised. The evaluation acknowledges that ultimately, achievement by SAICM relies on national governments having the political will to legislate for the sound management of chemicals and to ensure that such legislation is fully implemented.

Global Product Strategy (GPS)

The Global Product Strategy (GPS) was developed by the International Council of Chemical Associations (ICCA) as a global initiative to support and enhance the performance of the chemical industry globally. It has an important role in establishing uniform standards for communicating handling and product risks. The GPS is based on five pillars:

- Develop a base-set of hazard and exposure information to conduct safety assessments for chemicals in commerce;
- Undertake global GPS capacity building initiative to implement best risk assessment practices and management procedures, particularly with SMEs and in emerging and developing countries;
- Provide transparent access to science-based product safety information for the public and throughout the value chain;
- Promote stakeholder dialogue on science-based and risk-based chemicals management; and
- Broad commitment to the strategy: GPS is promoted and implemented by over 150 top chemical companies and more than 40 associations globally with the number of supporters continually growing.

The ICCA has established the GPS chemicals portal to provide the general public with access to reliable, science-based information on chemicals. The GPS safety summaries contained in the portal provide the most relevant product safety information from companies on the chemical products they manufacture using non-scientific language so that these can be easily understood. The portal provides access to the chemical safety summaries provided on company websites, which are designed to improve the safe handling and use of chemicals throughout the value chain.[279, 280]

Sustainability in industry

UNIDO Green Industry initiative for sustainable industrial development

The United Nations Industrial Development Organization (UNIDO) has developed a Green Industry Initiative (which was launched in 2009) in order to place sustainable industrial development in the context of global sustainable development challenges and contributes to the transition towards a green economy. The initiative is focused on enabling developing countries to achieve equitable

[278] Nurick, R. (2018): Independent Evaluation of the Strategic Approach from 2006 – 2015 Draft Report. Available at http://www.saicm.org/Portals/12/documents/meetings/IP2/IP_2_4_Independent_Evaluation.pdf

[279] EuroChem (2018): Global Product Strategy (GPS). Available at: http://www.eurochemgroup.com/en/global-product-strategy-gps/

[280] Cefic (2018): Product Stewardship. Available at: http://www.cefic.org/Industry-support/Responsible-Care-tools-SMEs/Product-stewardship/

economic growth that does not harm the environment, by creating conditions that allow industries to reduce pollution and resource use, while continuing to provide goods and employment.

As part of the Green Industry Initiative, UNIDO has developed a clear set of actionable strategies and approaches that can be used to advance progress towards an inclusive, low-carbon, safe and resource efficient green economy through promoting business-driven solutions. This framework of strategies, instruments, programmes and approaches are intended to remove gaps in the policy framework, in the support system and in the industrial sector's knowledge and skill-sets.[281] A key aspect of the initiative is ensuring the sound use of chemicals through preventative approaches and business models to assist enterprises in reducing the risk and impacts associated with chemical use. This includes control and management of hazardous chemicals to increase overall safety and protect workers, communities and the environment and includes substitution (i.e. replacing or reducing hazardous substances in products and processes with less hazardous or non-hazardous substances or by achieving an equivalent functionality through organisational or technological methods).[282]

As part of the Green Industry Initiative, UNIDO has assisted in developing (and plays a leading and coordinating role for the implementation of) the Chemical Leasing strategy which aims to provide benefits to both providers and users of chemicals by changing the basis of payment. Usually industries pay suppliers on the basis of the quantity of chemicals provided, which means that the supplier is interested in selling increasing quantities of chemicals. Under the Chemical Leasing model, the chemical supplier is paid for the service/function provided by the chemical rather than the quantity of chemical supplied. This encourages suppliers to reduce the amount of chemicals used and increase the recycling rate, leading to improved processes, increased safety and enhanced product quality. In November 2016, a legally non-binding joint declaration between UNIDO, Austria, Germany and Switzerland was signed with the aim of increasing awareness of chemical leasing at the political level and strengthening cooperation of the partners in global promotion activities.[283, 284]

X8.2.3 EU initiatives

Industry engagement

Social dialogue

At the European level, chemical industry social partners have come together to commit to social dialogue within the sector. This European sectoral social dialogue was initiated in 2002 after the creation of the European Chemical Employers Group. The European Mine, Chemical and Energy Workers' Federation (EMCEF) and the European Chemical Employers Group (ECEG) aimed to make use of the possibilities offered by European treaties and utilise this formalised dialogue in the interest of both the chemical industry and its workforce to foster development initiatives for the European chemical sector. In 2015 the scope of the sectoral social dialogue committee was officially enlarged

[281] UNIDO (2011): UNIDO Green Industry Initiative for Sustainable Industrial Development. United Nations Industrial Development Organization. Available at: http://www.greenindustryplatform.org/wp-content/uploads/2013/05/Green-Industry-Initiative-for-Sustainable-Industrial-Development.pdf

[282] Ibid

[283] Ibid

[284] UNIDO (2018): Chemical Leasing. United Nations Industrial Development Organization. Available at: https://www.unido.org/our-focus/safeguarding-environment/resource-efficient-and-low-carbon-industrial-production/chemical-leasing

with ECEG and the trade union industriAll Europe the recognised European social partners for the chemicals, pharmaceuticals, rubber and plastics industries.[285]

A framework of action was signed by ECEG and industriAll Europe on sustainable employment and career development in the European chemical sector. The purpose of this framework of action is to provide a European sectoral approach shared through national social partners in the chemical, pharmaceutical, plastics and rubber industries as a set of guidelines enabling national member organisations to deal effectively with challenges, including the promotion of safe and healthy workplaces and the well-being of workers. Social partners of the chemical industry aim to achieve these objectives through raising awareness, exchanging good practices and facilitating information exchange among members.[286, 287]

EU-OSHA Healthy Workplace Award

The European Agency for Safety and Health at Work (EU-OSHA) in combination with Member States has launched the Healthy Workplaces Campaign 2018-2019 in relation to the management of dangerous substances.[288] The purpose of this campaign is to raise awareness of worker exposure to hazardous chemicals and provide practical tools for minimising and, where possible, preventing this exposure. In line with its strategic objectives, the healthy workplaces campaign provides information, tools, special advice and support in a number of priority areas, including: awareness raising, managing risks, substitution, focussing on specific groups (such as women, young workers, migrant workers and temporary workers) and specific types of substances (such as carcinogens).

As part of the Healthy Workplaces Campaign the Good Practice Awards are used to recognise innovative safety and health practices in the workplace and to reward those organisations that introduce successful and sustainable initiatives for managing dangerous substances.[289] A range of resources have been developed to support the campaign, including a database of resources and tools, info sheets, case studies and a practical e-tool.

Surveillance and biomonitoring

EUROCAT

The European Surveillance of Congenital Anomalies (EUROCAT) is a network of population-based registries for the epidemiologic surveillance of congenital anomalies. The network consists of 43 registries across 23 countries and covers 29% of the European birth population (with more than 1.7 million births surveyed per year in Europe). The objectives of EUROCAT are[290]:

- To provide essential epidemiological information on congenital anomalies in Europe;
- To facilitate the early warning of new teratogenic exposures;
- To evaluate the effectiveness of primary prevention;
- To assess the impact of developments in prenatal screening;

[285] ECEG and industriAll (2017): European Chemical Industry Social Partners Roadmap 2015-2020. Available at: https://news.industriall-europe.eu/content/documents/upload/2017/12/636488401366011055_Roadmap_EN_web2.pdf

[286] Ibid

[287] Ibid

[288] EU-OSHA (2018): Healthy Workplaces Campaign 2018-2019 Manage Dangerous Substances. The European Agency for Safety and Health at Work. Available at: https://healthy-workplaces.eu/

[289] Ibid

[290] EUROCAT (n.d.): What is EUROCAT? Available at: http://www.eurocat-network.eu/aboutus/whatiseurocat/whatiseurocat

- To act as an information and resource centre for the population, health professionals and managers regarding clusters, exposures or risk factors of concern;
- To provide a ready collaborative network and infrastructure for research related to the causes and prevention of congenital anomalies and the treatment of effected children; and
- To act as a catalyst for the setting up of registries throughout Europe collecting comparable, standardised data.

Congenital anomaly registers are established to facilitate the identification of teratogenic exposures. Registers are also used for genetic studies and increasingly for research into the interaction of genetic and environmental factors in causing congenital anomalies. It is possible that this information could be combined with occupational data to identify links between congenital anomalies and occupational exposure to reprotoxic chemicals. This could perhaps be used to assist in the development of wider strategic approaches to controlling and, where possible, further reducing exposure to reprotoxins in the workplace. Such a possibility has been explored in the UK as part of the congenital anomaly recording process. Records of congenital anomalies are collected by the Office for National Statistics through the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS). The notification system aims to understand some risk factors for different anomalies through the collection of a range of social and demographic characteristics. Congenital anomaly notification is separate to birth registration; data is recorded by midwives and includes only partial demographic information. Occupation, for example, is poorly collected during the congenital anomaly notification process.

A study[291] proposing the linking of congenital anomaly records with corresponding birth records suggests that such an approach can improve the completeness of notified congenital anomalies whilst reducing the burden on data suppliers. Some information can be derived directly from the birth record, and eliminates the need to collect it again at congenital anomaly notification. This includes additional demographic information such as occupation, which is available as text for all birth records. Occupation data is particularly important for identifying the teratogenic effects of hazardous occupations. The linkage approach was found to be viable for 97% of records, improving both understanding of risk factors for congenital anomalies and the quality of congenital anomaly data. In order to pool information across a wider geographical area, NCARDRS data is shared with EUROCAT as part of the wider recording scheme for congenital anomalies, allowing comparisons to be made across Europe and the sharing of expertise.

HBM4EU

HBM4EU is a joint initiative (running for five years from 2017 to 2021) involving the EU-28 countries, the European Environment Agency and the European Commission and is co-funded under Horizon 2020. The aim of the initiative is to coordinate and advance human biomonitoring across Europe. This biomonitoring information will be used to assess human exposure to chemicals in Europe, to better understand the associated health impacts and to improve chemical risk assessment.[292]

Specific substances or groups of substances are selected to be subject to research at the European level. Therefore, it is important that HBM4EU addresses knowledge gaps on chemical exposure and resulting health impacts that have relevance at the European level and generates results that benefit European society. Priority is therefore given to substances that have been nominated by a significant proportion of partner countries. Substances that are exclusively of local or national concern are not

[291] Botting, B. & Abrahams, C. (2000): Linking congenital anomaly and birth records, Health Statistics Quarterly 08. Available at: https://www.ons.gov.uk/ons/rel/hsq/health-statistics-quarterly/no--8--winter-2000/linking-congenital-anomaly-and-birth-records.pdf

[292] HBM4EU (n.d.): About HBM4EU. Available at: https://www.hbm4eu.eu/about-hbm4eu/

prioritised under the initiative. The table below provides the first and second lists of substances prioritised under the HBM4EU initiative. The third round of prioritisation will occur for the 2019 to 2020 period.

Table X8-1: HBM4EU priority substances	
First list of HBM4EU priority substances	**Second list of HBM4EU priority substances**
• Aniline family • Bisphenols • Cadmium and chromium VI • Chemical mixtures • Emerging substances • Flame retardants • PAHs • Per-/poly-fluorinated compounds • Phthalates and Hexamoll® DINCH	• Acrylamide • Aprotic solvents • Arsenic • Diisocyanates • Lead • Mercury • Mycotoxins • Pesticides • Benzophenones
Source: HBM4EU (n.d.)[293]	

X8.2.4 National-level initiatives

Best practice in Member States

As discussed in Section X8.2.2, the success of international strategic approaches relies on national governments having the political will to legislate for the appropriate management of chemicals and to ensure that such legislation is fully implemented. Previous research[294] has identified a general awareness of the requirements of the CAD across Member States, although this awareness does not necessarily translate into adequate understanding by employers and employees. There are some countries in which extensive work is being undertaken into researching the issues involved in regulating the management of the risks of hazardous substances at work; notably Denmark, the Netherlands, Sweden and Finland. However, although many Member States have developed specific provisions to protect employees working with reprotoxic substances, the same study has identified that there are still many workplaces in which lack of awareness, poor knowledge and insufficient risk reduction/assessment are standard in relation to hazardous substances. Indeed, the report states that *'the total number of enterprises in most Member States have never performed a risk assessment in accordance with its meaning as understood in EU Directives, or if they have, they have not introduced any risk management measures as a result*'. Therefore, although heightened awareness of the need for risk management measures exists, with many examples of good practice, most notably in larger enterprises, this good practice on risk management of hazardous substances is not always translated into practice in smaller firms. Although a variety of tools and initiatives have been developed to support SMEs in the implementation of risk management, challenges still remain due to the availability of, and access to, support, the reach of regulation and the structure of the economy.

A recent study[295] in France has found substantial discrepancies in both occupational exposure levels and protection measures for carcinogenic, mutagenic and reprotoxic chemicals; whilst unskilled workers have the highest exposure intensities and levels, their protection level is inadequate.

[293] HBM4EU (n.d.): Substances. Available at: https://www.hbm4eu.eu/the-substances/

[294] Walters et al (2010): Contract to analyse and evaluate the impact of the practical implementation in the workplace of national measures implementing Directive 98/24/EC on Chemical Agents (project report). Available at: http://ec.europa.eu/social/BlobServlet?docId=10152&langId=en

[295] Havet et al (2018): Inequalities in the control of the occupational exposure in France to carcinogenic, mutagenic and reprotoxic chemicals, *European Journal of Public Health*

Conversely, managers and other professionals, who experienced lower CMR exposures, durations, and intensities than blue-collar workers, benefited the most from effective collective protections. Contrary to the above-mentioned research[296] which found that smaller firms may have poorer implementation of risk management, the French study found that availability of effective collective protection measures was not influenced by the size of the company. Although intervention of occupational health and safety officers in the past 12 months was associated with lower exposure intensity, it did not result in the implementation of more protection measures. Thus, at the workplace level, factors influencing practical implementation of measures are clearly complex and perhaps not easily remedied by existing national legislation.

A study undertaken by Milieu and RPA analysing the health, socioeconomic and environmental impacts associated with possible amendment to the Carcinogens and Mutagens Directive (2004/37/EC) identified voluntary measures and examples of best practice adopted in different Member States to reduce the risk to workers associated with exposure to reprotoxic substances. These are provided in the table below.

Table X8-2: National-level measures and examples of best practice to protect workers from reprotoxic substances in different Member States

Member State	Voluntary measures/initiatives	Examples of best practice
Austria	Ministry for Labour, Social and Consumer Protection Affairs provides support for the voluntary establishment of Safety and Health Management Systems	AUVA- Safety and Health Management System (SGM) - support available plus certification to introduce and implement the system. "Guidance and Collection of Examples related to the AUVA-SGM". Austrian NEARMISS Association (ANMA) offers support in analysing near accidents
Belgium	Provincial Committees for Work Promotion organise conferences, information campaigns and training. Several awareness raising tools are available	Range of tools to aid employers and workers. Makes use of multi-media to develop targeted tools, tailored to specific enterprises
Bulgaria	Collaborative agreement between the General Labour Inspectorate and the Confederation of Trade Unions for information exchange and the promotion of best practice	Checks on risk assessments, inspections of storage facilities, information exchange between committees on labour conditions
Cyprus	None identified	Cooperation between key stakeholders
Denmark	Voluntary accreditation scheme. One condition for accreditation: good practice regarding limitation of workers exposure to reprotoxic substances	No examples of best practice identified
Finland	The Nordic Institute for Advanced Training in occupational health provides training courses in reprotoxicity. Trade Union and cancer and health organisations involved in information campaigns	Guidance notes specifically on reprotoxic substances, training on reprotoxicity
France	Voluntary agreement between Ministry of Labour and three industry associations for better implementation of the legal requirements relating to workers' exposure	Setting up of a website platform for all professionals and employers engaged in a process of replacement of CMRs

[296] Walters et al (2010): Contract to analyse and evaluate the impact of the practical implementation in the workplace of national measures implementing Directive 98/24/EC on Chemical Agents (project report). Available at: http://ec.europa.eu/social/BlobServlet?docId=10152&langId=en

Table X8-2: National-level measures and examples of best practice to protect workers from reprotoxic substances in different Member States		
Member State	**Voluntary measures/initiatives**	**Examples of best practice**
	to CMRs	
Germany	Several public professional chambers adopted guidelines for the Implementation of Hazardous Substances Ordinance (no additional requirements but focus on better implementation)	Large pool of public institutes and agencies to develop risk management measures for occupational exposure to hazardous substances including CMRs. The Committee on Hazardous Substances and the Senate commission occupational exposure and biological limit values that go further than those adopted by the Commission. Development of technical rules and instruments to address specific risks in different sectors to make the legislation more comprehensive and user-friendly
Luxembourg	Benelux Charter for safety and health at work but not specifically dealing with exposure to reprotoxic substances at work	No examples of best practice identified
Netherlands	Labour conventions in order to address occupational hazards between employers, trade unions, employees and government covering exposure to hazardous substances but not specifically reprotoxic substances	No examples of best practice identified
Spain	The launch of the REPROTOX Initiative by a labour union Association	No examples of best practice identified
Sweden	Nordic Expert Group production of criteria documents on chemicals for occupational exposure limits. Not targeting reprotoxic substances	The Swedish Plastics and Chemicals Federation voluntary program for chemical industries for better security, health and environment. This relates to chemicals in general
UK	None identified	Good practice summarised under the 2005 survey on the control of task specific exposures to carcinogens, mutagens and reprotoxic substances in the UK chemical industry
Source: Milieu & RPA (2013)[297]		

Information has been obtained from stakeholders regarding the approaches taken to consider and deal with reprotoxic substances in certain Member States. Of the nine Member State authorities providing a response, six indicate that there are no specific requirements or conditions for substituting reprotoxic substances. Information received from Estonia, France and Sweden suggests that there are requirements relating to substitution of substances that are toxic to reproduction. However, it is also important to note that there are requirements (in line with the requirements of the CAD) for employers to undertake measures aimed at replacing chemical substances and mixtures with less hazardous (or non-hazardous) substances (with this covering substances that are carcinogenic, mutagenic and toxic to reproduction). It is also the case in some Member States (including Denmark and Germany) that where substitution of a chemical substance/mixture cannot be made then this should be documented and reported to the relevant authorities.

[297] Milieu & RPA (2013): Final Report for the analysis at EU-level of health, socioeconomic and environmental impacts in connection with possible amendment to Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens and mutagens at work to extend the scope to include category 1A and 1B reprotoxic substances.

Information received from Estonia indicates that substitution of a hazardous substance/mixture is the first option considered when a reprotoxic risk has been identified. Sweden and Poland have the same requirements for reprotoxic substances as for other hazardous substances (such as carcinogens), thus substitution is required where technically possible. Also, information received from a French authority indicates that the substitution principle is applicable to all hazardous substances, including those that are only classified as being toxic to reproduction. In the case of Latvia, according to the Cabinet Regulations No. 803, carcinogenic substances should be eliminated where possible through substitution with other substances, mixtures or processes that are less (or not) dangerous to the health and safety of employees. Where this is not possible, production and use of carcinogenic substances should be undertaken in a closed system to the extent technically feasible. However, this relates specifically to carcinogenic substances rather than reprotoxins.

It is important to note that some limitations to substitution have been identified by respondents. In the case of Cyprus, France and Sweden, where a risk has been identified for a substance and there is a possibility for this substance to be substituted then this should occur where technically feasible/achievable. The French authority also noted that there is a degree of flexibility in the case of enforcement where risk management measures are sufficient to control exposure (for instance implementation of a transition period for substitution in order to assist companies in adapting to this change).

In the case of Poland, employers are required to assess occupational risks, prepare an action plan and implement measures to safeguard workers from exposure to dangerous substances and preparations in accordance with Order No A1-457/V-961 of the Minister of Social Security and Labour and the Minister of Health 'On Approval of the General Provisions of Occupational Risk Assessment'. This is also the case in Denmark where collective risk management measures (such as closed systems and appropriate ventilation); restricted access to exposure areas and use of Personal Protective Equipment (PPE) should be considered and implemented as part of the workplace assessment in accordance with the Danish Executive Order. Cyprus, Estonia and France also note that it is necessary to trigger a range of implementation measures (including collective risk management measures, restricted access to exposure areas, health surveillance/monitoring and planning for unforeseen exposure) where a risk is identified for a substance. The French authority notes that these general principles are applicable for any hazardous chemical agent, with the implementation measures to be used selected on a case-by-case basis (i.e. focussing on those that are the most relevant). In Germany, the CMD, CAD and Asbestos Directive are incorporated into a single regulation (the Hazardous Substances Ordinance). Special provisions within this Regulation encompass exposure assessment, organisation precautions, PPE and prohibition of air recycling in exposure areas. In Sweden, CMR products are required to be handled in a closed system if technically possible. Where the system cannot be completely closed a series of measures should be taken to minimise worker exposure (including selection of equipment to reduce air contamination, requiring appropriate ventilation, use of PPE and housekeeping practices). Also, where CMR substances are used or likely to occur measures are required to be taken to ensure that only persons needed for the work can access these areas. It is also important to note that there are no specific requirements in Sweden for health surveillance/monitoring of workers exposed to reprotoxins.

Information received from Member State authorities indicates that many do not currently have specific procedures in the case of unforeseen/accidental exposure to reprotoxic substances. However, a Polish authority notes that, in the case of a chemical factor that poses a risk of exposure resulting from an accident in the work environment then the employer has a duty to develop and implement procedures of operation aimed at ensuring the protection of workers' health. These procedures should cover periodic rescue exercises, provisions of appropriate rescue measures and equipment. In Denmark, there are no specific legal procedures or requirements in relation to

unforeseen/accidental exposure to reprotoxic substances. However, Sections 20, 21 and 22 of the Danish Executive Order outline requirements for employers with regards to measures to prevent worker exposure to dangerous chemicals from accidents. There are also currently no specific procedures in France regarding accidental exposure to reprotoxic substances. However, the national legislation (R. 4412-33 to R. 4412-37 of the Labour Code) provides some principles and duties to employers who are required to be prepared to manage such situations (such as the use of alarm systems, training for workers, providing appropriate documentation and information (including for external bodies, such as the fire service etc.)). A similar situation occurs in Spain, where there are no specific requirements relating to reprotoxic substances, however, there are measures to be taken against accidents, incidents and emergencies related to hazardous chemical agents in general.

As part of the consultation process Member State authorities were asked whether there are specific requirements in their country regarding personal protective measures and personal hygiene requirements (e.g. restricting consumption of food in certain areas, separate washing facilities etc.) for reprotoxic substances. Nine Member State authority respondents indicate that while PPE must be used in situations where it is not possible to protect employees from exposure to hazardous substances through other (preventative) measures, there are no specific requirements relating to personal protection to substances that are toxic to reproduction. There are also no specific hygiene related requirements regarding reprotoxic substances. In Estonia and Sweden employers are required to prohibit eating, drinking and smoking in areas where there is a risk of contamination, provide appropriate clothing, separate storage for work and street wear, shower facilities and ensure that all PPE is checked and cleaned. These requirements are considered to apply to all hazardous substances, including those toxic to reproduction.

Member State authorities were also asked whether there are requirements within their country for the provision of information or training for workers and their participation in decision making with regards to reprotoxic substances. All nine authorities providing a response noted that there are no exclusive requirements that relate to reprotoxic substances in this regard. However, there are general requirements in place that relate to all hazardous substances. For example, in Poland there is an obligation for employers to provide workers with appropriate information, training and instructions on occupational health and safety when working with dangerous substances and mixtures, which refers to reprotoxic substances and mixtures. In Lithuania, according to the law on public health, persons that are employed and work with toxic substances must acquire knowledge in relation to the health impacts of using these substances and preventative actions to be taken in compliance with the requirements set out by the Ministry of Health. Where an employee refuses to complete a compulsory health training course, the employer is required to suspend the individual from work or, where possible, transfer them to another role that does not require compulsory health training knowledge. In, Denmark, reprotoxins are covered by the general rules on hazardous substances. According to these general rules the employer must make a workplace manual/instructions for the substances used (including the types of PPE to be used, where this can be found etc.). The employee should also receive effective training in the use of the substance. These general requirements also apply in other Member States.

Information received from Luxembourg indicates that the approach to enforcement taken by the authorities follows the enforcement regime outlined in the CAD and CMD and the performance of the inspections are also the same. In Germany enforcement of the Hazardous Substances Ordinance is the duty of the German Länder (states). The federal system in Germany includes 16 independent Länder, which means there are 16 different enforcement approaches adopted. Information received from a German authority notes that while there is no fixed difference in enforcement undertaken by the German states and the CAD and CMD, enforcement bodies in Germany can select their own key areas to focus on.

Further details of initiatives and strategic approaches implemented in different Member States is provided in the following sections.

France

On the 8th December 2015, the French Government and all representative social partners at the national level adopted the third Workplace health plan (for 2016-2020). This plan has two key objectives: 1) to reinforce a culture of risk prevention; and 2) to improve the quality of working conditions. This new plan was drafted on the basis of guidelines defined by the social partners represented on the Steering Committee on Working Conditions (COCT). The COCT includes representatives from trade unions and employer organisations, the Ministry of Labour and Ministry of Agriculture and the National Health Insurance Fund. The plan as three main objectives or areas of focus, which includes developing a prevention culture (including the tackling risks associated with the use of chemicals), improving quality of life in the workplace and reinforcing social dialogue.[298]

Also, in France the French national competence centre for industrial safety and environmental protection (INERIS) has established a national helpdesk providing operational support for companies interested in solutions to substitute bisphenols (BPA, BPS and BPF) in French and English. The website provides information on various families of molecules that are alternatives to bisphenols or alternatives to materials that require bisphenols along with examples of substitution and experiences in the supply chain.[299]

Italy

Collaboration with non-state actors is also occurring in Italy. As part of Italy's National Prevention Plan (2014-2018), the Italian Ministry of Health is collaborating with the Italian Society of Occupational Medicine for improvement in workplace health and safety.[300] The National Prevention Plan covers a broad expanse of subjects including workplace accidents and work related illnesses. On the 14th February 2018, a Memorandum of Understanding between the Italian Ministry of Health and the Italian Society of Occupational Medicine (SIML) was adopted to plan, promote and undertake joint activities to improve workers' health and safety conditions and to reduce health inequalities.[301]

Denmark

In 2013, the Danish Government established a broad agreement with all parliamentary parties on a series of chemicals initiatives for the period 2014 to 2017. The aim of the initiatives is to ensure that people can live without fear of becoming ill as a result of exposure to chemicals and that they can thrive in a healthy environment. The chemicals initiatives 2014-2017 are divided into three sections:

[298] Eurofound (2016): France – Social partners approve Workplace health plan for 2016-2020. European Foundation for the Improvement of Living and Working Conditions. Available at: https://www.eurofound.europa.eu/publications/article/2016/france-social-partners-approve-workplace-health-plan-for-2016-2020

[299] INERIS (n.d.): National Helpdesk – Bisphenols substitution. The French national competence centre for industrial safety and environmental protection. Available at: https://substitution-bp.ineris.fr/en/documents

[300] Ministero della Salute (2018): Piano Nazionale della Prevenzione 2014-2018. Available at: http://www.salute.gov.it/imgs/C_17_pubblicazioni_2285_allegato.pdf

[301] Ministero della Salute (2018): Protocollo di Intesa. Available at: http://www.salute.gov.it/imgs/C_17_notizie_3292_listaFile_itemName_0_file.pdf

1) international collaboration; 2) non-toxic products; and 3) circulating resources.[302, 303]. Some of the initiatives include targeting work to include substances of very high concern (SVHC) on the REACH candidate list with a view to phasing out and substitution of the substances, developing tools to obtain knowledge regarding hazardous chemicals (including knowledge to help enterprises substitute hazardous chemicals in their production processes), focussing on global phase-out of substances of concern such as endocrine disruptors and substances of concern in articles and establishing a chemicals forum to facilitate dialogue between stakeholders, ensure good communication and identify new solutions.

Denmark is also investing in a new three-year initiative (from 2018 to 2021) that aims to protect vulnerable groups from harmful chemicals, which will include strengthening research into hormone-disrupting substances and providing more information to consumers in order to better inform them of products containing harmful chemicals.[304]

Germany

In Article 4.2 of the CMD, companies are required to provide (upon request) information setting out how substitution of a chemical was considered to the relevant authorities. On transposing the Directive into national legislation, Germany (in the case of implementing Article 4.2 of the CMD) has adopted a strategic approach that requires companies to provide detailed documentation to enforcement bodies on request. This includes reasons for decisions taken not to substitute a substance for a less hazardous alternative (Hazardous substances ordinance §6(8)3, § 18(3)).

The REACH Regulation requires registrants of substances to carry out exposure assessments with the aim of identifying exposure conditions and associated risk management measures that enable the safe use of a chemical. Within this process there is no hierarchy of control in terms of the risk management measures to be adopted. The CAD and CMD both outline hierarchies to be followed by the employer in order to ensure protection of worker safety. In some Member States, this hierarchy has been expanded upon as part of a strategic approach towards the protection of workers. For example, in Germany the CAD has been transposed with the inclusion of restrictions on the extent to which an OEL can be met through the use of respiratory protection equipment. Permanent use of this equipment is not permitted, thus the OEL is required to be met without its use.

United Kingdom

The Health and Safety Executive (HSE) publishes data[305] on proceedings instituted by HSE and, in Scotland, the Crown Office and Procurator Fiscal Service under specific regulations, including the Control of Lead at Work Regulations (2002). Data provided includes number of convictions, details of

[302] Ministry of Environment and Food of Denmark (n.d.): Chemicals Initiatives 2014-17 – towards a life without toxins. Available at: http://kemikalieindsatsen.dk/english/indledning/

[303] Ministry of Environment and Food of Denmark – Environmental Protection Agency (2017): Effect Assessment of the Chemicals Initiatives 2014-2017. Available at: https://www2.mst.dk/Udgiv/publications/2017/11/978-87-93614-34-5.pdf

[304] ChemicalWatch (2017): Denmark launches three year chemicals initiative. Available at: https://chemicalwatch.com/61923/denmark-launches-three-year-chemicals-initiative

[305] HSE (2018) Prosecution activity by HSE and, in Scotland, the Crown Office and Procurator Fiscal Service (COPFS) 2012/13 to latest year: Table 5: Proceedings instituted by HSE and, in Scotland, the Crown Office and Procurator Fiscal Service under specific regulations and acts by prosecution outcomes 2016/17. Available at: http://www.hse.gov.uk/statistics/tables/index.htm#lead

legislation violations and fines imposed. The public register of prosecutions may act as a deterrent against regulation violations.

Non EU Initiatives

Brazil is currently developing a national policy on industrial chemicals that should be issued by the end of 2018. The draft legislation was initially approved by the National Commission on Chemical Safety (Conasq), which is comprised of representatives of the federal government, the Brazilian Entity Association for Environmental Studies (Abema), industry, NGOs and university representatives.[306] Conasq representatives are currently reviewing and considering all comments submitted during the public consultation, and will provide justifications for accepting or rejecting suggestions for changes to the draft legislation.

In Japan, the Expert Committee under the Ministry of Health, Labor and Welfare (MHLW) is responsible for making recommendations that can modify workplace safety law. It is currently discussing the adoption of individual samplers in the Working Environmental Assessment. One of the primary functions of the Committee is to review information provided by NGOs - such as TLV/TWA and STEL by American Conference of Governmental Industrial Hygienists (ACGIH) and OELs by the Japan Society of Occupational Health (JSOH) – in order to review current Administrative Concentration Levels.[307]

X8.3 Voluntary industry initiatives

X8.3.1 Overview

Our approach to this sub-task has involved the following:

- Sub-task 2.6a: Identifying and providing descriptions of voluntary initiatives likely to have an impact on exposure of workers to CMR substances;
- Sub-task 2.6b: Identifying the common themes and approaches across initiatives and where they add value and complement each other and legislation for the substances concerned.

The aim has been to identify product stewardship and other voluntary initiatives, as well as relevant social partner agreements. The work has involved internet searches to identify relevant initiatives at the global level and EU level, as well as consultation via the targeted questionnaire to collect more detailed data.

X8.3.2 Sectoral initiatives

Coatings Care

The international care and sustainability programme for the coatings industry (also known as Coatings Care) is a global umbrella programme for the paint and printing ink manufacturing industries. The objective of the Coatings Care initiative is to improve the performance of the coatings industry in the fields of safety, health, environment, distribution and product stewardship. It is a voluntary initiative that describes good practices and offers participating companies the opportunity to pursue a common, effective management approach for their health, safety and environmental programmes

[306] Ministério do Meio Ambiente (2018): Comissão Nacional de Segurança Química. Available at: http://www.mma.gov.br/seguranca-quimica/comissao-nacional

[307] http://www.mhlw.go.jp/file/05-Shingikai-11201000-Roudoukijunkyoku-Soumuka/0000197082.pdf

and provides advice on achieving high standards through self-assessment and measurement of performance. The programme is being actively implemented by paint, printing ink and adhesives companies in more than 10 countries. The Coatings Care programme is fully compatible with the chemical industry's Responsible Care Programme (further discussed in Section X8.3.4), but the codes of guidance have been developed specifically for the needs of the coatings industry.[308, 309]

Five key areas of management responsibility (namely manufacturing, transport and distribution, training, product stewardship and community responsibility) are covered by the codes of management practice under the Coatings Care initiative.[310] The main benefits of the Coatings Care programme are considered to include assisting companies to make efficient use of resources in complying with health, safety and environmental regulations, pursuing a common management approach for health, safety and environmental programmes, increasing learning and identifying/evaluating areas for improvement.[311]

Industry information on health safety and environmental performance trends demonstrate that the Coatings Care programme has been effective in facilitating improvements within the sector. Over the past few decades the positive contribution of the Coatings Care programme has been recognised by others outside of the industry, including government institutions and insurance companies.[312, 313]

It is also important to note that the members of the European Council of the Paint, Printing Ink and Artists' Colours Industry (CEPE) have committed themselves to the principle of product stewardship, including the voluntary removal or substitution of hazardous substances whenever unacceptable risks to human health or the environment are identified. An example of this is the CEPE exclusion list for printing inks and related products. CEPE recognise that the Coatings Care and Responsible Care codes of practice assist paint and printing ink manufacturers in developing safer and more sustainable products.[314]

Safety in the hairdressing sector

In April 2012, UNI Europa and the employers' organisation Coiffure EU signed a framework agreement on a series of aims designed to improve occupational health and safety protection in the sector. The agreement dealt also with the working environment, safety standards, staff training, and the

[308] BCF (2018): Coatings Care. The British Coatings Foundation. Available at: https://www.coatings.org.uk/BCF_Matters/Coatings_Care.aspx

[309] AkzoNobel (n.d.): Product Stewardship. Available at: https://www.akzonobel.com/en/about-us/what-we-do/sustainability/our-approach/our-strategy/our-policies/product-stewardship

[310] BCF (2018): Codes of Practice. The British Coatings Foundation. Available at: https://www.coatings.org.uk/Coatings_Care/Codes_of_Practice.aspx

[311] CPCA (n.d.): The Benefits of Coatings Care. Canadian Paint and Coatings Association. Available at: http://www.canpaint.com/the-benefits-of-coatings-care/

[312] BCF (2018): Coatings Care - Performance. The British Coatings Foundation. Available at: https://www.coatings.org.uk/Public/Coatings_Care_Performance.aspx

[313] CPCA (n.d.): Coatings Care – The Canadians Paint Industry's Health, Safety and Environment Initiative. Canadian Paint and Coatings Association. Available at: http://www.canpaint.com/coatings-care/

[314] CEPE (2004): Imagine a world without colour – The impact of REACH on the paint, printing ink and artists' colours industry and some proposed solutions. Available at: http://www.aptintas.pt/media/apftv_pt_legislacao_reach_CEPE_REACH_BROCHURE.pdf

harmonisation of working conditions (in relation, for example, to the handling of cosmetic products, measures to prevent harm to the respiratory tract, etc.).[315]

The agreement aims at building an integrated approach for the prevention and reduction of occupational safety and health risks for workers in the hairdressing sector, especially skin problems and musculoskeletal disorders, through the application of the principles of risk assessment, risk management and prevention.

The framework agreement, amongst others, contains several measures to limit hairdresser workers exposure to chemical agents. It provides that the mixing or transferring of chemical substances that can generate hazardous gases, fumes or particulates shall take place at special workstations that have an appropriate complementary ventilation system. It also mentions that the principle of substitution must apply to the following materials (permanent wave compositions containing thioglycolic acid ester, hair cosmetics releasing dust, powdered natural rubber latex gloves, tools which can transfer nickel to the skin). Finally, it requires that workers must wear suitable protective gloves when applying dyes, tints and blonding agents, and also when preparing mixing or transferring chemical substances.[316]

Consultation responses indicate that the agreement was also signed by BusinessEurope, UEAPME, CEEP and ETUC (and the liaison committee Eurocadres/CEC) in 2012, however, has not yet been acted upon by the European Commission.

French industrial initiatives

At Member State level, France is a leader in NGO participation in the development of voluntary industry standards in the field of CMR restriction. The Union of Chemical Industries (UIC) signed an agreement for the prevention of risks associated with CMR substances with the Ministry of Labour, INRS (National Institute for Research and Security) and CNAMTS (National Fund for Health Insurance of Employees) to testify to the commitment of the chemical industry to act to improve CMR risk prevention, both at its own sites and at its customers.[317] The agreement includes the development of information and communication on the provisions of the labour code relating to the prevention of CMR risks and their implications. The collaboration between the signatories essentially concerns two points: firstly, the development of a common chemical risk assessment method (SEIRICH); and secondly, organisation of chemical risk prevention training specifically designed for small and medium-sized enterprises (SME) and individual contractors.[318]

German Trade Association Raw Materials and Chemical Industry

The Berufsgenossenschaft Rohstoffe und chemische Industrie (BG RCI) is a professional association for the raw materials and chemical industry, and is a part of the German social security. They are a statutory accident insurance agency and responsible for around 32,000 member companies with approximately 1.4 million employees, providing advice and support to the mining, building materials,

[315] ETUI (2016): Union campaign criticises Commission apathy towards hairdressers' health. European Trade Union Institute. Available at: https://www.etui.org/Topics/Health-Safety-working-conditions/News-list/Union-campaign-criticises-Commission-apathy-towards-hairdressers-health

[316] Commission paritaire de la coiffure et des soins de beauté n° 314. Available at: http://www.emploi.belgique.be/CAO/314/314-2012-000644.pdf

[317] Union des Industries Chimiques.

[318] INRS (2014): Prevention des risques chimiques et CMR. Available at: http://www.inrs.fr/dms/inrs/PDF/document-reference-formation-risques-chimiques-cmr2017/document-reference-formation-risques-chimiques-cmr2017.pdf

quarrying, chemical industry, leather industry, papermaking and equipment industries as well as sugar in all matters relating to occupational health and safety.

The BG RCI has produced a leaflet "Reprotoxic substances" which provides information about regulations and directives and provides a list of reprotoxic substances. It is aimed at workers and employers, managers and supervisors.

The leaflet contains in its Annex 1 a list of known reprotoxic substances. Information on the German MAK and BAT Values List 2015 are included (Substances of Group C of the German MAK and BAT Values List 2015) in Annex 2 as well as substances toxic to breast-fed infants in Annex 3[319].

Italian industrial initiatives

In 2016, the Tuscany North Confindustria (a group of 30 Italian companies) have collectively joined the Greenpeace Detox commitments. Members include companies coming from the chemicals, raw materials and textile sector, with the latter including yarn dyeing plants, yarn mills, fabric dyeing plants and fabric mills. Consultees to this study note that the Detox Project promotes eco-sustainability, with this including within its mission the reduction of the use of carcinogenic and reprotoxic chemicals. Examples of activities undertaken as part of the project include an analysis of dyestuffs used in textile production and identification of the potential chemical contaminants within these, including phthalates, ethoxylated alkylphenols, aromatic amines and chlorophenols. 228 dyestuffs were analysed with 112 found to be contaminated with alkylphenols, 128 contaminated with aromatic amines, 28 contaminated with chlorophenols and 7 with phthalates including DBP and DEHP.[320] It is clear that this first piece of research is now being followed by other investigations, and that the aim is to reduce the presence of such substances in dyestuffs.

X8.3.3 Substance specific initiatives

Voluntary initiatives in relation to lead

The International Lead Association (ILA) has established a voluntary employee blood lead reduction programme, known as the Lead Action 21 programme. The Lead Action 21 Plan specifies as part of its charter that operations are managed responsibly and safely to continually reduce the impact to human health and the adoption of best practice is encouraged.[321] Enrolment into the programme and demonstration of continuous improvement are a condition of membership of the ILA.

The Lead Action 21 (LA21) programme itself provides a focus for Members to share past, present and future initiatives designed to encourage and embed the principles of sustainable development throughout the lead producing world. It sets out to[322]:

[319] BG RCI (2015): Fruchtschädigende Stoffe Informationen für Mitarbeiterinnen und betriebliche Führungskräfte. Berufsgenossenschaft Rohstoffe und chemische Industrie. Available at: http://downloadcenter.bgrci.de/resource/downloadcenter/downloads/M039_Gesamtdokument.pdf

[320] Giuseppe B., Andrea F., Riccardo D. (2016): Dyestuffs for Fashion Industry – actual chemical contamination levels. BuzziLab and Consorzio Italiano Implementazione Detox. Available at: https://www.confindustriatoscananord.it/media/DETOX/Case%20study%20coloranti_ENG.pdf

[321] International Lead Association (2018): LA21 Charter. Available at: https://www.ila-lead.org/responsibility/la21-charter

[322] International Lead Association (2018): Lead Action 21 0 Environmental and social responsibility for the 21st century. Available at: https://www.ila-lead.org/responsibility/lead-action-21

- **Inform** - share knowledge of the safe production, use and recycling of lead and its contribution to life in the 21st century; share best practice to ensure the highest levels of protection for human health and the environment and make the highest standards the norm – everywhere;
- **Support** - build on the work of the International Lead Management Center and use its expertise to provide practical help and guidance to countries, in the developing world and those in transition, that need it; and
- **Improve** - put measures in place for continuous improvement.

Sectoral targets are established with the latest being zero employees exceeding a blood lead content of 20µg/dL. These targets have been particularly effective in reducing lead exposure in the sector and at the end of the last phase of the programme, which had a target of zero employees exceeding 30µg/dL by the end of 2016, there was a 65% reduction in number of employees exceeding this target compared to the 2013 baseline. The ILA voluntary programme also highlights the reproductive toxicity concerns with exposure of women to lead and recommends that blood lead levels of females of reproductive capacity (defined as ≤45 years of age or as agreed by the company medical advisor) be maintained below 10µg/dL.

As part of the initiative, the ILA has produced a number of guidance notes for reducing occupational exposure to lead, and has set ten golden rules for good practice. These are:[323]

- Plant workers must wear designated clothes, that are provided by their employer in the workplace;
- Wear clean work wear every day or shift and change during the working day if necessary;
- Wear appropriate fit tested and properly maintained respiratory equipment, and/or apply the correct ventilation;
- Always shower after the end of every shift and whenever potential contamination risks have been high;
- Do not take work wear home for cleaning or washing;
- Adopt work practices that minimise or mitigate occupational exposure to lead;
- Segregate work areas from administrative offices and eating areas;
- Ensure that drinking and eating areas are always clean and lead free;
- Always wash hands and face and scrub nails prior to eating at the workplace; and
- Never smoke at work.

In addition, as lead is specifically referenced in the EU Pregnant Workers Directive, all companies are mandated to follow procedures established in National implementation.[324]

ELSIA (the European Lead Sheet Association) also has in place a Product Stewardship Program for reducing occupational exposure to lead.[325] The final code of practice for the Product Stewardship includes the following for occupational lead exposure[326]:

[323] International Lead Association (2018): Guidance Notes. Available at: https://www.ila-lead.org/responsibility/guidance-notes

[324] European Commission (1992): Council Directive 92/85/EEC of 19 October 1992 on the introduction of measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or are breastfeeding (tenth individual Directive within the meaning of Article 16 (1) of Directive 89/391/EEC). Available at: http://eur-lex.europa.eu/legal-content/EN/NIM/?uri=CELEX:31992L0085

[325] European Lead Sheet Association (undated): Product Stewardship. Available at: https://elsia.org.uk/product-stewardship/

[326] European Lead Sheet Association (2018): Product Stewardship Final Code of Practice. Available at: https://elsia.org.uk/wp-content/uploads/2018/04/Code-of-Practice-18.pdf

- For manufacturing: The blood lead of all exposed workers are to be monitored to ensure compliance with a level of 40 µg/dl (REACH DNEL) and 10 µg/dl for women;
- For manufacturing: To commit to having no employees exceeding a blood lead level of 20mcg/dL with the next target of the program being to have no employees exceeding a blood lead level exceeding 25 mcg/dL by the end of 2019;
- For sales outlets and distribution channels: label all lead sheets "professional use only"; provide access to the appropriate safety data sheets;
- For sales outlets and distribution channels: Provide access to the appropriate risk management advice for handling lead sheet;
- For downstream users: Have safety data sheets available on websites for professional users to have easy access to them;
- For downstream users: Provide training materials including risk management measures for professional users; and
- For downstream users: To highlight the importance of regular blood lead sampling of professional workers and to promote the reduction of blood lead levels.

The ten golden rules for handling lead sheet are the same as those of the ILA and employers should also ensure that adequate washing and changing facilities are provided, any air lead monitoring requirements are being fulfilled, workforce health surveillance (for example periodic blood level measurements) are performed and respirators (for example a dust mask) and other protective clothing such as gloves and overalls are provided.[327]

A leadworker safety guide is supplied for installing lead sheets.[328] The advice is to: apply a barrier cream before starting work; always wear gloves when handling lead; ensure masks are clean and fit properly and check filters or use disposable masks; always wear a mask when working with lead; beards can prevent masks sealing properly; don't smoke when working with lead; never eat or drink when working with lead; keep your hands away from your face; don't bite your fingernails and keep them short; use tissues rather than a handkerchief; handle dusty overalls with care; remove work wear before leaving the site; wash hands and face thoroughly before eating and smoking and before you leave work; use heavy duty hand wipes if running water is not available; always wash overalls separately; and make sure your blood lead levels are tested at least once a year if working with lead.

Crystalline silica

Although a carcinogen rather than a reproductive toxin, the NEPSI **Agreement on Workers Health Protection through the Good Handling and Use of Crystalline Silica and Products** containing it was put forward by consultees as an example of best practice with respect to gaining the multi-sector support[329] for developing guidelines on good practice for worker protection purposes. The aim of the agreement is to:

- To protect the health of employees and other individuals occupationally exposed at the workplace to respirable crystalline silica from materials/products/raw materials containing crystalline silica;

[327] European Lead Sheet Association (undated): Health & Safety. Available at: https://elsia.org.uk/product-stewardship/health-safety/

[328] European Lead Sheet Association (undated): Leadworker Safety. Available at: http://elsia.wpengine.com/wp-content/uploads/2014/04/ELSIA-LeadworkerSafetyDoc-UK.pdf

[329] Including the International Bureau for Precast Concrete, the European Foundry Association, the Council of European Employers of the Metal, Engineering and Technology-based

- To minimise exposure to respirable crystalline silica at the workplace by applying good practices stipulated herein in order to prevent, eliminate or reduce occupational health risks related to respirable crystalline silica; and
- To increase the knowledge about potential health effects of respirable crystalline silica and about good practices.

Good practices are defined in the Agreement as the general principles of the Framework Directive and of Section II of the CAD are further developed and illustrated by Annex 1 to the Agreement.[330] This Agreement mentions that the Parties acknowledge that the general principles of the Framework Directive, and of the CAD remain at all times applicable (including, in particular, risk assessment; risk prevention; specific protection and prevention measures; arrangements to deal with accidents, incidents and emergencies; information and training for workers). No coherence issues are identified here since this agreement complements the CAD and specifies certain measures for workers exposed to crystalline silica.

The Good Practice Guide, which acts as the main instrument for the application of the Agreement, provides tools to progressively improve workers protection, to enhance compliance with EU Member States' existing workers health and safety legislation and to increase knowledge of the potential effects of respirable crystalline silica. It includes detailed task sheets, along with an introduction on crystalline silica and the risk assessment procedure. These provide a set of detailed technical recommendations to reduce exposure in the specific industrial settings encountered in each of the signatory industries.[331]

X8.3.4 Other industry initiatives

This section discusses the main industry-wide initiatives relating to product stewardship and the chemical industry's Responsible Care programmes which exist within both the EU and the US.

Product Stewardship

Product stewardship initiatives promote the safe handling and use of chemicals at all stages in the life cycle, from research and development, to manufacture, sale, use and final disposal with the aim of ensuring that neither people nor the environment are harmed. Strictly speaking, this requires manufacturers and users of chemicals to understand the hazards associated with chemical products and to ensure that those hazards are managed in a manner that minimises risks. As an initiative, product stewardship essentially reinforces legislative requirements, especially in the EU with respect to OSH, REACH and other legal obligations.

There are a number of guideline documents available to assist different actors within the chemical supply chain to manage risks and improve performance in relation to safety, health and the environment. For example, Cefic and the European Association of Chemical Distributors (Fecc) have developed guidelines on product stewardship in the supply chain[332], which describe how health, safety and environmental responsibilities can be shared between suppliers and distributors so that both can deliver their product stewardship and responsible care commitments throughout the product

[330] NEPSI (2018): The European Network on Silica. Available at: https://www.nepsi.eu/nepsi
[331] NEPSI (2018): The Good Practice Guide. Available at: https://www.nepsi.eu/good-practice-guide
[332] Cefic and Fecc (2012): Product Stewardship in the Supply Chain – Joint Cefic/Fecc Product Stewardship Guidelines. Available at: http://www.cefic.org/Documents/IndustrySupport/RC%20tools%20for%20SMEs/Document%20Tool%20Box/Product-Stewardship-in-the-Supply-Chain-2012.pdf?epslanguage=en

lifecycle. This is also supplemented by a guide developed by Fecc[333] providing examples of good product stewardship practices aimed at chemical distributors.

Responsible Care

Both Cefic and the American Chemistry Council have established the Responsible Care programme with the aim of improving environmental health, safety and security performance. It is a global chemical industry initiative with aims similar to those of product stewardship initiatives more generally. Responsible Care commits companies, national chemical industry associations and their partners to[334]:

- Continuously improve the environmental, health, safety and security knowledge and performance of technologies, processes and products over their life cycles so as to avoid harm to people and the environment;
- Use resources efficiently and minimise waste;
- Report openly on performance, achievements and shortcomings;
- Listen, engage and work with people to understand and address their concerns and expectations;
- Cooperate with governments and organisations in the development and implementation of effective regulations and standards, and to meet or go beyond them; and
- Provide help and advice to foster the responsible management of chemicals by all those who manage and use them along the product chain.

The initiative was launched in Canada in 1985 in order to address public concerns regarding the manufacture, distribution and use of chemicals. The Responsible Care programme has since been adopted in nearly 60 economies across the world. Evaluations of the earlier years of the Responsible Care program did not find the initiative to be effective, due to a lack of appropriate implementation, monitoring, and reporting procedures.[335,336] However, independent third party certification was introduced as compulsory in 2005 to improve avoidance and program outcomes.[337] The Responsible Care Global Charter was launched in 2006 and extends the process of continuous improvement to include other activities (in addition to those related to chemicals manufacturing) associated with the safe use and handling of products along the value chain. At the global level, Responsible Care is addressed by the International Council of Chemical Associations (ICCA).

Each chemical company that implements the Responsible Care initiative is expected to collect and report data for a core set of environmental, health and safety performance measures. Also, each national association is expected to collect, collate and report this data from its members in each

[333] Fecc (2013): Fecc Guide with Good Practices for Chemical Distributors Product Stewardship. Available at: http://www.cefic.org/Documents/IndustrySupport/RC%20tools%20for%20SMEs/Document%20Tool%20Box/Guide-with-Good-Practices-for-Chemical-Distributors-ProductStewardship.pdf?epslanguage=en

[334] Cefic (2018): Responsible Care – The chemical industry's commitment to sustainability. Available at: http://www.cefic.org/Responsible-Care/

[335] King, A. and Lenox, M., (2000): Industry self-regulation without sanctions: the chemical industry's Responsible Care Program. Academy of Management Journal, 43: 698–716

[336] Gamper-Rabindran S. and Finger, S. (2013): Does self-regulation reduce pollution? Responsible Care in the chemicals industry, Journal of Regulatory Economics, 43: 1-30

[337] Vidovic, et al. (2013): Third Party Certification and the Effectiveness of Voluntary Pollution Abatement Programs: Evidence from Responsible Care. Agricultural and Applied Economics Association 2013 Annual Meeting, August 4–6, 2013, Washington, DC

country.[338] In 2010, Cefic and its member federations adopted to European Care Security Code with Cefic's role being to advance Responsible Care in Europe and ensure consistency of implementation by national member federations. Each member federation is responsible for developing and running its own national Responsible Care programme with its member companies and to oversee implementation.[339]

ChemSec Business Group

The ChemSec Business Group is a non-profit collaboration between companies to encourage concrete progress on toxic use reduction of chemicals. The group gathers together market-leading companies, across a diversity of sectors, to develop effective corporate practice in the substitution of hazardous chemicals. In addition, it raises public awareness of companies' efforts and progress in relation to this issue. The business group establishes a forum for downstream enterprises (using chemical substances), such as retailers, manufacturers of consumer goods etc., that are working together to reduce the use of toxic substances in products. These companies have either expressed interest in supporting stricter chemicals legislation and/or are actively seeking to avoid the use of hazardous substances in production of their products (e.g. in response to consumer demand or in line with business priorities).[340]

The ChemSec Business Group has also been actively involved in developing the SIN List, which contains Substances of Very High Concern (SVHCs) in accordance with criteria outlined in the EU REACH Regulation. The SIN List is available as an online database and contains substances that are Carcinogenic, Mutagenic or toxic to Reproduction (CMRs), substances that are Persistent, Bioaccumulative and Toxic or very Persistent and very Bioaccumulative (PBTs and vPvBs) and substances of equivalent level of concern.[341]

Broader voluntary initiatives

There are also product stewardship programs for handling chemicals, such as Cefic's Product Stewardship program for safe chemical management, however no specific measures regarding reprotoxins are provided.[342]

X8.3.5 Tools and information sources

As part of the risk assessment and management process there is a need for companies to select the most appropriate measures for controlling exposure to hazardous substances (including reprotoxins). These measures should also be regularly updated as a result of technical progress and should take account of unforeseen higher exposures (e.g. those that may occur during maintenance or incidents).

[338] Cefic (2009): Responsible Care Global Charter. Available at: http://www.cefic.org/Documents/ResponsibleCare/RC_GlobalCharter2006%5b1%5d.pdf

[339] Cefic (2018): Responsible Care – The chemical industry's commitment to sustainability. Available at: http://www.cefic.org/Responsible-Care/

[340] ChemSec (n.d.): ChemSec Business Group. Available at: http://chemsec.org/business-and-investors/chemsec-business-group/

[341] ChemSec (2014): ChemSec Business Group – Dialogue for Sustainable Business. Available at: http://chemsec.org/wp-content/uploads/2016/03/Chemsec_Business_Group_140227.pdf

[342] Cefic (2018): Product Stewardship. Available at: http://www.cefic.org/Industry-support/Responsible-Care-tools-SMEs/Product-stewardship/

A range of established tools are available to assist companies in undertaking risk assessments relating to hazardous chemicals. Four of the most well-known tools are[343]:

- **International Chemical Control Toolkit of the International Labour Organisation (ILO)**: This toolkit outlines a scheme for protection of workers from dangerous chemicals and is designed for use by SMEs in developing countries. This includes a number of guidance sheets relating to specific substances and types of risks, with these providing details of risk management measures to be undertaken to control occupational exposure[344];

- **COSHH-Essentials**: This toolkit consists of 'control guidance sheets' and include industry specific 'direct advice sheets' and 'generic control guidance sheets' that provide information and advice on how to control exposure to hazardous substances in the workplace[345];

- **EMKG (Einfaches Massnahmenkonzept Gefahrstoffen)**: EMKG is a workplace control scheme for hazardous substances, which is designed to be used by SMEs to support the assessment of risks when dealing with hazardous substances and provides appropriate control measures[346].

- **Stoffenmanager®**: This is an online tool to help company managers and employees of SMEs and large organisations to identify and prioritise chemical hazards and measures to control workplace exposures. The tool consists of modules for conducting a risk assessment such as control banding, quantitative exposure assessment and REACH worker exposure assessment.[347, 348]

The first three tools are control banding tools that direct the user to a class ('band') of control measures as well as links to sectoral or process-related guidance. The Stoffenmanager tool enables a qualitative as well as (for inhalation exposure) a quantitative risk assessment and the effectiveness of specific control measures can also be assessed using the same tool.

Substitution of chemicals with those that are less hazardous or non-hazardous is one way of reducing exposure (to workers, consumers and the wider environment) to hazardous substances. The ability to collect and assess data on alternative substances/processes is an important aspect of the substitution process, with several tools available to facilitate comparison between substances. Some examples include:

- **Column model for chemical substitutes assessment**: The Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA) developed a column model to provide industry with a practical tool for identification of alternative substances. This is a

[343] OSHWiki (2017): Hierarchy of controls applied to dangerous substances. Available at: https://oshwiki.eu/wiki/Hierarchy_of_controls_applied_to_dangerous_substances#.E2.80.98Best_practice.E2.80.99_or_.E2.80.98evidence-based.E2.80.99_practice

[344] ILO (2017): International Chemical Control Toolkit. International Labour Organization. Available at: http://www.ilo.org/legacy/english/protection/safework/ctrl_banding/toolkit/icct/index.htm

[345] HSE (n.d.): COSHH Essentials. Health and Safety Executive. Available at: http://www.hse.gov.uk/coshh/essentials/index.htm

[346] BAuA (n.d.): Easy-to-use Workplace Control Scheme for Hazardous Substances (EMKG). Federal Institute for Occupational Safety and Health. Available at: https://www.baua.de/EN/Topics/Work-design/Hazardous-substances/EMKG/Easy-to-use-workplace-control-scheme-EMKG_node.html

[347] Stoffenmanager®7 (n.d.): What is Stoffenmanager®? Available at: https://stoffenmanager.nl/

[348] OSHWiki (2017): Stoffenmanager® for smart chemicals management and business continuity. Available at: https://oshwiki.eu/wiki/Stoffenmanager%C2%AE_for_smart_chemicals_management_and_business_continuity

simplified method to make a preliminary comparison between the risks of different substances and products and offers an initial judgement on the convenience of substitution. The model is based on six columns in which the following hazard categories are described: acute health hazards, chronic health hazards, fire and explosion hazards, environmental hazards, exposure potential and process hazards.[349]

- **Technical Rules for Hazardous Substances (TRGS 600)**: The German Hazardous Substances Ordinance (GefstoffV) states that the employer has the duty to determine, test and decide on substitution of hazardous substances and to document it. TRGS 600 is intended to: 1) support the employer in avoiding activities involving hazardous substances, 2) to replace hazardous substances by substances, mixtures or processes that are not hazardous or less hazardous under the relevant use conditions, and 3) to replace hazardous processes with less hazardous ones. TRGS 600 includes a framework for deciding on substitution that considers criteria for assessing technical suitability, health and physicochemical risk of alternatives.[350, 351]

- **Quick scan**: Quick Scan is a screening method developed by the Dutch Ministry of Housing, Spatial Planning and Environment to ensure that the potential risks and hazards associated with the use of substances in each stage of their life cycle are sufficiently controlled so as to remove, or reduce to a negligible level, any harmful effects caused by substances on human health and the environment. The tool describes measures to be taken for each chemical depending on their intrinsic hazard and potential exposure.[352]

- **GISBAU – support for the safe use of chemicals in the construction industry (Germany)**: GISBAU is an information system designed to reduce the risks from construction chemicals and to provide support to SMEs within the construction industry. It offers comprehensive information about dangerous chemicals used in building, reconditioning and cleaning, including operating instructions, guidance and brochures related to different work activities and a coding system (Giscode).[353]

- **Green Screen for Safer Chemicals**: This is a method of comparative chemical hazard assessment that can be used for identifying chemicals of high concern and safer alternatives. The tool sets threshold values for hazards based on (eco)toxicological data or the hazard classification of substances. Combinations of different types of hazards and their level assigned according to the thresholds are used to rank a substance in terms of its use (i.e. whether a substance should be avoided because it is a chemical of high concern).[354]

- **Pollution Prevention Options Analysis System (P2OASys)**: This was designed by the Toxic Use Reduction Institute of Massachusetts (TURI) to provide companies with a framework for complete and systematic evaluation of potential hazards of processes and products and of

[349] Subsport (n.d.): Column Model for Chemical Substitutes Assessment. Substitution Support Portal. Available at: https://www.subsport.eu/substitution-tools/column-model-for-chemical-substitutes-assessment

[350] Subsport (n.d.): Technical Rules for Hazardous Substances (TRGS) 600 "Substitution". Available at: https://www.subsport.eu/substitution-tools/trgs-600

[351] BAUA (n.d.): Technical Rules for Hazardous Substances (TRGS) – Selected TRGS. Available at: https://www.baua.de/EN/Service/Legislative-texts-and-technical-rules/Rules/TRGS/TRGS.html

[352] Subsport (n.d.): Quick Scan. Available at: https://www.subsport.eu/substitution-tools/quick-scan

[353] European Agency for Safety and Health at Work (2003): Systems and Programmes – How to convey OSH information effectively, the case of dangerous substances. Available at: https://osha.europa.eu/en/tools-and-publications/publications/reports/312

[354] GreenScreen (2018): About GreenScreen®. Available at: https://www.greenscreenchemicals.org/about

alternatives. The tool can be used to systematically examine potential worker and environmental impacts of options to reduce the use of toxic chemicals as well as comparing options to reduce the use of hazardous chemicals based on quantitative and qualitative factors. It can be used to analyse technological processes, chemical substances and mixtures.[355]

There are also a range of information sources available to assist companies in substituting hazardous substances/mixtures for those that are not hazardous or less hazardous. These include:

- **SUBSPORT**: is a multilingual platform for information exchange on alternative substances and technologies and also provides tools and guidance for substances evaluation and substitution management[356];

- **CLEANTOOL**: is a Europe wide database for parts cleaning, metal surface cleaning, component cleaning and degreasing based on processes used by European companies[357].

- **RISCTOX**: is a database of hazardous substances developed to provide organised and concise information about the health and environmental risks caused by chemicals contained in products generally used or handled by companies[358].

- **Substitution-CMR**: is a database available in French providing examples of alternatives to CMR substances and is aimed at professionals who wish to initiate the process of substitution[359].

- **BASTA**: is a database for the construction sector, containing products that pass BASTA criteria regarding health and the environment and is targeted towards organisations and individuals within the construction sector that wish to select products that contain less hazardous substances[360].

[355] SUBSPORT (n.d.): Pollution Prevention Options Analysis System (P2OASys). Available at: https://www.subsport.eu/substitution-tools/p2oasys

[356] SUBSPORT (n.d.): About the Portal. Substitution Support Portal. Available at: https://www.subsport.eu/about-the-portal

[357] CLEANTOOL (n.d.): The Project. Available at: https://www.cleantool.org/home-3/das-projekt/?lang=en

[358] RISCTOX (n.d.): RISCTOX – a comprehensive database on toxic and hazardous substances. Available at: https://risctox.istas.net/en/

[359] EU-OSHA (2017): Practical tools and guidance – substitution-cmr.fr. Available at: https://healthy-workplaces.eu/en/tools-and-publications/practical-tools/substitution-cmrfr

[360] BASTA (2018): About BASTA. Available at: https://www.bastaonline.se/about-basta/about-basta/?lang=en

Annex 9 Further Information on the Shortlisting of Substances

X9.1 Step 1: Identify all substances with CLH or CLI self-classification for Reprotoxic 1A/1B or 2 and categorise and sequentially trim lists by:

- Whether registered under REACH or not (reasoning: substances not registered are not permitted for use over 1 t per year);
- Whether registered under REACH and CLH or CLI self-classification for Reprotoxic 1A/1B (reasoning: R2 classifications are not in scope);
- Whether REACH registration is full, intermediate or NONS (reasoning: type of registration has a bearing on likely levels of exposure and exposure routes);
- Whether the Reprotoxic 1A/1B classification is a CLH or has been drawn from self-classifications on the CLI (reasoning: self-classifications drawn from the CLI are unreliable and need to be checked substance by substance); and
- Whether the substances are restricted/authorised under REACH or not (reasoning: substances which are restricted/authorised are subject to tighter controls and vice versa).

Statistics on the numbers of substances categorised by the above are provided below.

Table X9-1: All substances with CLH or CLI self-classification for R 1A/1B or 2

Type	Registration status	Type of registration	Type of classification for R	Restrictions/authorisations	Classifications (note that substances may have self-classifications on the CLI at 2 as well as 1a/1b)						
					Number of substances	C 1A/1B	C2	M 1A/1B	M2	R 1A/1B	R2
R 1A/1B/2	Registered and non-registered	n/a	CLH and Self class		3,142	508	435	254	395	621	2,930
R 1A/1B/2	Not registered under REACH	n/a	CLH and Self class		2,160	212	318	86	250	427	2,040
R 1A/1B/2	Registered under REACH	All	CLH and Self class		982	296	117	168	145	194	890
R2	Registered under REACH	All	CLH and Self class		788	253	79	160	105	0	788
R 1A/1B	Registered under REACH	All	CLH and Self class		194	43	38	8	40	194	102
		Full registration	R Based on CLH	Restricted/authorised	14	3	1	0	0	14	n/a

Table X9-1: All substances with CLH or CLI self-classification for R 1A/1B or 2												
Type	Registration status	Type of registration	Type of classification for R	Restrictions/authorisations	Classifications (note that substances may have self-classifications on the CLI at 2 as well as 1a/1b)						
					Number of substances	C 1A/1B	C2	M 1A/1B	M2	R 1A/1B	R2
				Not restricted/authorised	51	17	0	0	18	51	n/a
			R Based on Self class	n/a (none restricted/authorised)	48	12	12	4	6	48	n/a
		Intermediate only	R Based on CLH	n/a (none restricted/authorised)	12	3	1	0	3	12	n/a
			R Based on Self class	Restricted/authorised	1	1	0	1	1	1	n/a
				Not restricted/authorised	53	6	21	3	9	53	n/a
		NONS	R Based on CLH	Restricted/authorised	1	0	0	0	1	1	n/a
				Not restricted/authorised	14	1	3	0	2	14	n/a

X9.2 Step 2: Divide the lists of substances with CLH or CLI self-classification for Reprotoxic 1A/1B or 2 (as in Table 1) into substances which:

- Also have a classification for C1a/1b or M1a/1b (reasoning: these substances are already within the scope of the CMD); and
- Do not also have a classification for C1a/1b or M1a/1b (reasoning: these substances are not within the scope of the CMD).

Statistics on the numbers of substances categorised by the above are provided in the tables below. The substances which are of potential interest (and go on to further screening) are highlighted in grey in Table X9-3 and are substances which:

- Have a CLH or CLI self-classification for Reprotoxic 1A/1B but do not also have a classification for C1a/1b or M1a/1b (reasoning: these substances are not within the scope of the CMD); and
- Are registered under REACH or not (reasoning: *substances not registered are not permitted for use over 1 t per year*).

Table X9-2: All substances with CLH or CLI self-classification for R 1A/1B or 2 and also for C or M 1a/1b												
Type	Registration status	Type of registration	Type of classification for R	Restrictions/authorisations	Classifications (note that substances may have self-classifications on the CLI at 2 as well as 1a/1b)						
					Number of substances	C1A/1B	C2	M1A/1B	M2	R1A/1B	R2
R 1A/1B/2	Registered and non-registered	n/a	CLH and Self class		539	508	95	254	191	164	456
R 1A/1B/2	Not registered under REACH	n/a	CLH and Self class		238	212	61	86	114	119	179
R 1A/1B/2	Registered under REACH	All	CLH and Self class		301	296	34	168	77	45	277
R2	Registered under REACH	All	CLH and Self class		256	253	22	160	49	0	256
R 1A/1B	Registered under REACH	All	CLH and Self class		45	43	12	8	28	45	21
		Full registration	R Based on CLH	Restricted/authorised	3	3	0	0	0	3	n/a
				Not restricted/authorised	17	17	0	0	16	17	n/a
			R Based on Self class	n/a (none restricted/authorised)	13	12	6	4	4	13	n/a
		Intermediate only	R Based on CLH	n/a (none restricted/authorised)	3	3	0	0	3	3	n/a
			R Based on Self class	Restricted/authorised	1	1	0	1	1	1	n/a
				Not restricted/authorised	7	6	6	3	3	7	n/a
		NONS	R Based on CLH	Restricted/authorised	0	0	0	0	0	0	n/a
				Not restricted/authorised	1	1	0	0	1	1	n/a

Table X9-3: All substances with CLH or CLI self-classification for R1a/1b or 2 but not for C or M 1a/1b												
Type	Registration status	Type of registration	Type of classification for R	Restrictions/authorisations	Classifications (note that substances may have self-classifications on the CLI at 2 as well as 1a/1b)						
					Number of substances	C1A/1B	C2	M1A/1B	M2	R1A/1B	R2
R 1A/1B/2	Registered and non-registered	n/a	CLH and Self class		2,604	0	340	0	204	458	2,474
R 1A/1B/2	Not registered under REACH	n/a	CLH and Self class		1,922	0	257	0	136	308	1,861
R 1A/1B/2	Registered under REACH	All	CLH and Self class		681	0	83	0	68	149	613
R2	Registered under REACH	All	CLH and Self class		532	0	57	0	56	0	532
R 1A/1B	Registered under REACH	All	CLH and Self class		149	0	26	0	12	149	81
		Full registration	R Based on CLH	Restricted/authorised	11	0	1	0	0	11	n/a
				Not restricted/authorised	34	0	0	0	2	34	n/a
			R Based on Self class	n/a (none restricted/authorised)	35	0	6	0	2	35	n/a
		Intermediate only	R Based on CLH	n/a (none restricted/authorised)	9	0	1	0	0	9	n/a
			R Based on Self class	Restricted/authorised	0	0	0	0	0	0	n/a
				Not restricted/authorised	46	0	15	0	6	46	n/a
		NONS	R Based on CLH	Restricted/authorised	1	0	0	0	1	1	n/a
				Not restricted/authorised	13	0	3	0	1	13	n/a

X9.3 Step 3: Confirm that substances with a self-classification for R1/a1b from the CLI are so classified by:

Opening each substance profile page on ECHA's website;

- For fully registered substances[361] checking whether the substance:

[361] Note that, for fully registered substances toxicological data specified in Annex VII to X of REACH must be supplied and classifications made according to the CLP made on the basis of this up to date information and so all fully registered substances will have an up to date classification from the dossier. In contrast, there are reduced information requirements for intermediate only substances and so absence of a reach dossier classification is not a reliable indication that a substance is not R1a/1b.

- has a Reprotoxic 1A/1B classification derived from notifications from REACH dossiers – in which case it can be regarded as a certain Reprotoxic 1A/1B substance and is **retained in the list**;
- does not have a Reprotoxic 1A/1B classification derived from REACH dossiers – in which case it can be regarded as not a Reprotoxic 1A/1B substance based on the most up to date information in dossiers and is **removed from the list**.

- For intermediate substances[361] checking whether the substance:

  - has a Reprotoxic 1A/1B classification derived from notifications from REACH dossiers – in which case it can be regarded as a certain Reprotoxic 1A/1B substance and is **retained in the list**;
  - does not have a Reprotoxic 1A/1B classification derived from REACH dossiers but a significant proportion of the other CLI notifications do identify Reprotoxic 1A/1B classification – in which case it can be regarded as a likely/possible Reprotoxic 1A/1B substance for the purposes of the study and is **retained in the list**;
  - does not have a Reprotoxic 1A/1B classification derived from REACH dossiers and few other CLI notifications identify Reprotoxic 1A/1B classification – in which case it can be regarded as unlikely to be/not a Reprotoxic 1A/1B substance for the purposes of the study and is **removed from the list**.

Statistics on the substances that have been removed from the list are provided in Table X9-4 and a list of the removed substances is provided below.

Table X9-4: REACH registered substances with no CLH or confirmed CLI self-classification for R 1A/1B

Type	Registration status	Type of registration	Type of classification for R	Restrictions/authorisations	Classifications (note that substances may have self-classifications on the CLI at 2 as well as 1a/1b)						
					Number of substances	C1A/1B	C2	M1A/1B	M2	R 1A/1B	R2
R 1A/1B	Fully registered	Full registration	R Based on CLH	Restricted/authorised	0	0	0	0	0	0	n/a
				Not restricted/authorised	1	0	0	0	0	0	n/a
			R Based on Self class	n/a (none restricted/authorised)	16	0	1	0	0	16	n/a
		Intermediate only	R Based on CLH	n/a (none restricted/authorised)	0	0	0	0	0	0	n/a
			R Based on Self class	Restricted/authorised	0	0	0	0	0	0	n/a
				Not restricted/authorised	17	0	4	0	1	17	n/a
		NONS	R Based on CLH	Restricted/authorised	0	0	0	0	0	0	n/a
				Not restricted/authorised	0	0	0	0	0	0	n/a

Table X9-5: Substances removed because R 1A/1B classification is not confirmed

Fully registered substances removed because REACH dossier classification is not R 1A/1B

Table X9-5: Substances removed because R 1A/1B classification is not confirmed			
EC Number	**CAS Number**	**Name**	**Brief profile page**
200-064-1	50-78-2	O-acetylsalicylic acid	https://echa.europa.eu/brief-profile/-/briefprofile/100.000.059
203-919-7	111-90-0	2-(2-ethoxyethoxy)ethanol	https://echa.europa.eu/brief-profile/-/briefprofile/100.003.563
204-317-7	119-36-8	Methyl salicylate	https://echa.europa.eu/brief-profile/-/briefprofile/100.003.925
205-251-1	136-53-8	Zinc bis(2-ethylhexanoate)	https://echa.europa.eu/brief-profile/-/briefprofile/100.004.774
205-391-3	140-01-2	Pentasodium (carboxylatomethyl) iminobis(ethylenenitrilo)tetraacetate	https://echa.europa.eu/brief-profile/-/briefprofile/100.004.902
209-062-5	554-13-2, 7439-93-2	Lithium carbonate	https://echa.europa.eu/brief-profile/-/briefprofile/100.008.239
209-502-6	583-39-1	Benzimidazole-2-thiol	https://echa.europa.eu/brief-profile/-/briefprofile/100.008.640
210-088-4	605-50-5	Diisopentyl phthalate	https://echa.europa.eu/brief-profile/-/briefprofile/100.009.172
214-189-4	1112-39-6	Dimethoxydimethylsilane	https://echa.europa.eu/brief-profile/-/briefprofile/100.012.900
215-575-5	1332-77-0, 12045-78-2	Dipotassium tetraborate	https://echa.europa.eu/brief-profile/-/briefprofile/100.014.160
231-891-6	7775-19-1, 10555-76-7	Sodium metaborate, anhydrous	https://echa.europa.eu/brief-profile/-/briefprofile/100.028.992
234-371-7	11128-29-3	Potassium pentaborate	https://echa.europa.eu/brief-profile/-/briefprofile/100.031.234
234-521-1	12007-89-5, 12046-04-7	Diammonium decaborate	https://echa.europa.eu/brief-profile/-/briefprofile/100.031.370
237-731-1	13951-70-7	11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione	https://echa.europa.eu/brief-profile/-/briefprofile/100.034.287
240-347-7	16219-75-3	5-ethylidene-8,9,10-trinorborn-2-ene	https://echa.europa.eu/brief-profile/-/briefprofile/100.036.664
263-064-0	61789-51-3	Naphthenic acids, cobalt salts	https://echa.europa.eu/brief-profile/-/briefprofile/100.057.313
270-844-4	68478-92-2	Platinum, 1,3-diethenyl-1,1,3,3-tetramethyldisiloxane complexes	https://echa.europa.eu/brief-profile/-/briefprofile/100.064.384

Intermediate registered substances removed because REACH dossier classification is not R 1A/1B and few other CLI notifications identify R 1A/1B				
EC Number	**CAS Number**	**Name**	**Brief profile page**	**% CLI notifications R 1A/1B**
200-004-4	50-03-3	Hydrocortisone 21-acetate	https://echa.europa.eu/brief-profile/-/briefprofile/100.000.005	2%
200-020-1	50-23-7	Hydrocortisone	https://echa.europa.eu/brief-profile/-/briefprofile/100.000.019	3%
200-268-0	56-35-9	Bis(tributyltin) oxide	https://echa.europa.eu/brief-profile/-/briefprofile/100.000.244	11%
202-675-9	98-51-1	4-tert-butyltoluene	https://echa.europa.eu/brief-profile/-/briefprofile/100.002.433	<1%
204-471-5	121-45-9	Trimethyl phosphite	https://echa.europa.eu/brief-profile/-/briefprofile/100.004.065	1%
211-148-2	630-93-3	Phenytoin sodium	https://echa.europa.eu/brief-profile/-/briefprofile/100.010.136	12%
211-560-2	665-66-7	Amantadine hydrochloride	https://echa.europa.eu/brief-profile/-/briefprofile/100.010.511	1%
219-243-0	2392-39-4	Dexamethasone 21-(disodium phosphate)	https://echa.europa.eu/brief-profile/-/briefprofile/100.017.495	17%

Table X9-5: Substances removed because R 1A/1B classification is not confirmed				
237-099-7	13614-98-7	[4S-(4α,4aα,5aα,12aα)]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxonaphthacene-2-carboxamide monohydrochloride	https://echa.europa.eu/brief-profile/-/briefprofile/100.033.712	2%
239-346-4	15307-79-6	Sodium [2-[(2,6-dichlorophenyl)amino]phenyl]acetate	https://echa.europa.eu/brief-profile/-/briefprofile/100.035.754	1%
239-784-6	15687-27-1	Ibuprofen	https://echa.europa.eu/brief-profile/-/briefprofile/100.036.152	3%
244-838-7	22204-53-1	Naproxen	https://echa.europa.eu/brief-profile/-/briefprofile/100.040.747	3%
257-950-6	52485-79-7	Buprenorphine	https://echa.europa.eu/brief-profile/-/briefprofile/100.052.664	<1%
271-363-2	68551-11-1	1-Propene, hydroformylation products, high-boiling	https://echa.europa.eu/brief-profile/-/briefprofile/100.064.856	<1%
429-400-7	199327-61-2	7-methoxy-6-(3-morpholin-4-yl-propoxy)-3H-quinazolin-4-one	https://echa.europa.eu/substance-information/-/substanceinfo/100.102.775	<1%
604-045-2	137862-53-4	(2S)-3-methyl-2-(N-{[2'-(1H-1,2,3,4-tetrazol-5-yl)-[1,1-biphenyl]-4-yl]methyl}pentanamido)butanoic acid	https://echa.europa.eu/brief-profile/-/briefprofile/100.113.097	5%
610-965-5	53123-88-9	(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[(1R)-2-[(1S,3R,4R)-4-hydroxy-3-methoxy cyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]-oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone	https://echa.europa.eu/brief-profile/-/briefprofile/100.107.147	1%

X9.4 Step 4: Set out final list of substances of high relevance

Statistics on the REACH registered substances with a CLH or a confirmed CLI self-classification for Reprotoxic 1A/1B (but none for C or M 1a/1b) are provided in Table 6.

In terms of relevance:

- Substances that are fully registered are likely to have the highest volumes of use and number of uses. Information describing uses is available from dossiers for fully registered substances – these substances are the most relevant for the study;
- Information on volumes of use and types is not available for NONS and so there is limited scope for exploring these substances further – these substances have little potential for further study and so are of low relevance;
- Substances registered only as intermediates have only limited intermediate uses with low/no potential for exposure. There is no data on use volumes. Here too there is limited potential for further study.

A full list of the substances is provided below.

Table X9-6: REACH registered substances with CLH or confirmed CLI self-classification for R 1A/1B but not for C or M 1a/1b

Type	Registration status	Type of registration	Type of classification for R	Restrictions/authorisations	Classifications (note that substances may have self-classifications on the CLI at 2 as well as 1a/1b)						
					Number of substances	C1A/1B	C2	M1A/1B	M2	R 1A/1B	R2
R 1A/1B	Fully registered	Full registration	R Based on CLH	Restricted/authorised	10	0	1	0	0	10	n/a
				Not restricted/authorised	34	0	0	0	2	34	n/a
			R Based on Self class	n/a (none restricted/authorised)	18	0	5	0	2	18	n/a
		Intermediate only	R Based on CLH	n/a (none restricted/authorised)	9	0	1	0	0	9	n/a
			R Based on Self class	Restricted/authorised	0	0	0	0	0	0	n/a
				Not restricted/authorised	30	0	11	0	5	30	n/a
		NONS	R Based on CLH	Restricted/authorised	1	0	0	0	1	1	n/a
				Not restricted/authorised	13	0	3	0	1	13	n/a

Table X9-7: Identities of REACH registered substances with CLH or confirmed CLI self-classification for R 1A/1B but not for C or M 1a/1b

Type	EC no.	CAS	Name	Total tonnage Band	Restr.	Auth.	Cand. list	CORAP	Indicative OEL
Full registration- R Based on CLH - Restricted/authorised n=10									
CLH	201-245-8	80-05-7	4,4'-isopropylidenediphenol	1000000 - 10000000 tpa	Y	-	Y	Y	Y
CLH	201-553-2	84-69-5	Diisobutyl phthalate	0 - 10 tpa	-	Y	Y	-	-
CLH	201-557-4	84-74-2, 93952-11-5	Dibutyl phthalate	1000 - 10000 tpa	Y	Y	Y	-	-
CLH	201-622-7	85-68-7	Benzyl butyl phthalate	1000 - 10000 tpa	Y	Y	Y	-	-
CLH	203-445-0	106-94-5	1-bromopropane	1000 - 10000 tpa	-	Y	Y	-	-

Table X9-7: Identities of REACH registered substances with CLH or confirmed CLI self-classification for R 1A/1B but not for C or M 1a/1b									
Type	**EC no.**	**CAS**	**Name**	**Total tonnage Band**	**Restr.**	**Auth.**	**Cand. list**	**CORAP**	**Indicative OEL**
CLH	203-924-4	111-96-6	Bis(2-methoxyethyl) ether	100 - 1000 tpa	-	Y	Y	-	-
CLH	204-118-5	115-96-8	Tris(2-chloroethyl) phosphate	0 - 10 tpa	-	Y	Y	-	-
CLH	204-211-0	117-81-7	Bis(2-ethylhexyl) phthalate	10000 - 100000 tpa	Y	Y	Y	-	-
CLH	231-100-4	7439-92-1	Lead	1000000 - 10000000 tpa	Y	-	-	-	-
CLH	231-106-7	7439-97-6	Mercury	100 - 1000 tpa	Y	-	-	-	-
Full registration - R Based on CLH - Not restricted/authorised n=43									
CLH	200-679-5	68-12-2	N,N-dimethylformamide	10000 - 100000 tpa	-	-	Y	-	Y
CLH	200-842-0	75-12-7	Formamide	10 - 100 tpa	-	-	Y	-	-
CLH	201-039-8	77-58-7	Dibutyltin dilaurate	100 - 1000 tpa	-	-	-	-	-
CLH	201-182-6	79-16-3	N-methylacetamide	Confidential	-	-	Y	-	-
CLH	201-545-9	84-61-7	Dicyclohexyl phthalate	100 - 1000 tpa	-	-	-	Y	-
CLH	201-861-7	88-85-7	Dinoseb	1000 - 10000 tpa	-	-	Y	-	-
CLH	202-506-9	96-45-7	Imidazolidine-2-thione	100 - 1000 tpa	-	-	Y	-	-
CLH	202-625-6	97-99-4	Tetrahydrofurfuryl alcohol	100 - 1000 tpa	-	-	-	-	-
CLH	202-696-3	98-73-7	4-tert-butylbenzoic acid	100 - 1000 tpa	-	-	-	-	-
CLH	203-713-7	109-86-4, 109-87-5	2-methoxyethanol	1000 - 10000 tpa	-	-	Y	-	-
CLH	203-794-9	110-71-4	1,2-dimethoxyethane	100 - 1000 tpa	-	-	Y	-	-
CLH	203-804-1	110-80-5	2-ethoxyethanol	100 - 1000 tpa	-	-	Y	-	Y
CLH	203-977-3	112-49-2	1,2-bis(2-methoxyethoxy)ethane	10 - 100 tpa	-	-	Y	-	-
CLH	204-826-4	127-19-5	N,N-dimethylacetamide	10000 - 100000 tpa	-	-	Y	-	Y
CLH	205-711-1	148-24-3	Quinolin-8-ol	0 - 10 tpa	-	-	-	-	-
CLH	206-019-2	288-32-4	Imidazole	10+ tpa	-	-	-	Y	-
CLH	206-104-4	301-04-2, 6080-56-4	Lead di(acetate)	0 - 10 tpa	-	-	Y	-	-
CLH	211-128-3	630-08-0	Carbon monoxide	1000 - 10000 tpa	-	-	-	-	Y
CLH	211-670-0	683-18-1	Dibutyltin dichloride	10 - 100 tpa	-	-	Y	-	-
CLH	212-828-1	872-50-4	1-methyl-2-pyrrolidone	10000 - 100000 tpa	-	-	Y	-	Y
CLH	215-125-8	1303-86-2	Diboron trioxide	1000 - 10000 tpa	-	-	Y	-	-
CLH	215-540-4	1303-96-4, 1330-43-4, 12179-04-3	Disodium tetraborate, anhydrous	100000 - 1000000 tpa	-	-	Y	-	-

Table X9-7: Identities of REACH registered substances with CLH or confirmed CLI self-classification for R 1A/1B but not for C or M 1a/1b									
Type	**EC no.**	**CAS**	**Name**	**Total tonnage Band**	**Restr.**	**Auth.**	**Cand. list**	**CORAP**	**Indicative OEL**
CLH	220-250-6	2687-91-4	1-ethylpyrrolidin-2-one	100 - 1000 tpa	-	-	-	-	-
CLH	233-139-2	10043-35-3	Boric acid	100000 - 1000000 tpa	-	-	Y	-	-
CLH	234-390-0	10332-33-9, 11138-47-9, 12040-72-1, 37244-98-7	Perboric acid, sodium salt	10000 - 100000 tpa	-	-	Y	-	-
CLH	234-541-0	12008-41-2, 12280-03-4	Disodium octaborate	1000 - 10000 tpa	-	-	-	-	-
CLH	236-542-1	13424-46-9	Lead diazide	10 - 100 tpa	-	-	Y	-	-
CLH	239-290-0	15245-44-0	Lead 2,4,6-trinitro-m-phenylene dioxide	10 - 100 tpa	-	-	Y	-	-
CLH	239-622-4	15571-58-1	2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate	1000 - 10000 tpa	-	-	Y	-	-
CLH	246-677-8	25155-23-1	Trixylyl phosphate	100 - 1000 tpa	-	-	Y	Y	-
CLH	310-154-3	121158-58-5	Phenol, dodecyl-, branched	10000 - 100000 tpa	-	-	-	Y	-
CLH	400-600-6	71868-10-5	2-methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one	1000 - 10000 tpa	-	-	-	-	-
CLH	407-330-8	61571-06-0	Tetrahydrothiopyran-3-carboxaldehyde	Confidential	-	-	-	-	-
CLH	425-970-6	3724-43-4	Chloro-N,N-dimethylformiminium chloride	1+ tpa	-	-	-	-	-
Full registration - R Based on Self class - none restricted/authorised, n= 19									
Self	200-683-7	68-26-8	Retinol	0 – 10 tpa	-	-	-	-	-
Self	201-228-5	79-81-2	Retinyl palmitate	100 – 1000 tpa	-	-	-	-	-
Self	201-289-8	80-54-6	2-(4-tert-butylbenzyl)propionaldehyde	1000 - 10000 tpa	-	-	-	Y	-
Self	211-995-8	734-32-7	Estr-4-ene-3,17-dione	0 - 10 tpa	-	-	-	-	-
Self	212-449-1	818-08-6	Dibutyltin oxide	1000 - 10000 tpa	-	-	-	-	-
Self	212-977-2	897-06-3	Androsta-1,4-diene-3,17-dione	10 - 100 tpa	-	-	-	-	-
Self	213-934-0	1067-53-4	Tris(2-methoxyethoxy)vinylsilane	1000 - 10000 tpa	-	-	-	-	-
Self	220-481-2	2781-10-4	Dibutyltin bis(2-ethylhexanoate)	10 - 100 tpa	-	-	-	-	-
Self	235-252-2	12141-20-7	Trilead dioxide phosphonate	100000 - 1000000 tpa	-	-	Y	-	-
Self	236-813-4	13494-80-9	Tellurium	100 - 1000 tpa	-	-	-	-	-
Self	248-227-6	27107-89-7	2-ethylhexyl 10-ethyl-4-[[2-[(2-ethylhexyl)oxy]-2-oxoethyl]thio]-4-octyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate	1000 - 10000 tpa	-	-	-	Y	-

Table X9-7: Identities of REACH registered substances with CLH or confirmed CLI self-classification for R 1A/1B but not for C or M 1a/1b									
Type	**EC no.**	**CAS**	**Name**	**Total tonnage Band**	**Restr.**	**Auth.**	**Cand. list**	**CORAP**	**Indicative OEL**
Self	250-882-8	31981-44-9	17-hydroxy-19-norpregn-4-ene-3,20-dione 17-acetate	0 - 10 tpa	-	-	-	-	-
Self	259-048-8	54261-67-5	Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate)	10 - 100 tpa	-	-	-	-	-
Self	272-233-8	68784-25-8	Phenol, dodecyl-, sulfurized, carbonates, calcium	100 – 1000 tpa	-	-	-	-	-
Self	272-234-3	68784-26-9	Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased	10000 - 100000 tpa	-	-	-	Y	-
Self	272-486-4	68855-45-8	Phenol, dodecyl-, sulfurized, calcium salts	1000 - 10000 tpa	-	-	-	Y	-
Self	306-115-5	96152-43-1	Phenol, dodecyl-, branched, sulfurized	100 - 1000 tpa	-	-	-	-	-
Self	601-329-8	114798-26-4	[2-butyl-4-chloro-1-({4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl]phenyl}methyl)-1H-imidazol-5-yl]methanol	100 - 1000 tpa	-	-	-	-	-
Self	608-209-4	284461-73-0	4-(4-((((4-CHLORO-3-(TRIFLUOROMETHYL)PHENYL)AMINO)CARBONYL)AMINO) PHENOXY)-N-METHYL-2-PYRIDINECARBOXAMIDE	10 - 100 tpa	-	-	-	-	-
Intermediate only - R Based on CLH - none restricted/authorised, n=9									
CLH	200-855-1	75-26-3	2-bromopropane	Intermediate Use Only	-	-	-	-	-
CLH	201-377-6	81-81-2	Warfarin	Intermediate Use Only	-	-	-	-	-
CLH	202-716-0	98-95-3	Nitrobenzene	Intermediate Use Only	-	-	Y	-	Y
CLH	203-867-5	111-41-1	2-(2-aminoethylamino)ethanol	Intermediate Use Only	-	-	-	-	-
CLH	204-624-6	123-39-7	N-methylformamide	Intermediate Use Only	-	-	-	-	-
CLH	210-894-6	625-45-6	Methoxyacetic acid	Intermediate Use Only	-	-	Y	-	-
CLH	425-150-8	94723-86-1	2-butyryl-3-hydroxy-5-thiocyclohexan-3-yl-cyclohex-2-en-1-one	Intermediate Use Only	-	-	-	-	-
CLH	427-230-8	5571-36-8	cyclic 3-(1,2-ethanediylacetale)-estra-5(10),9(11)-diene-3,17-dione	Intermediate Use Only	-	-	-	-	-
Intermediate only - R Based on Self class - none restricted/authorised, n= 30									
Self	200-003-9	50-02-2	Dexamethasone	Intermediate Use Only	-	-	-	-	-
Self	200-171-3	53-36-1	Methylprednisolone 21-acetate	Intermediate Use Only	-	-	-	-	-
Self	200-186-5	53-86-1	Indometacin	Intermediate Use Only	-	-	-	-	-
Self	201-476-4	83-43-2	Methylprednisolone	Intermediate Use Only	-	-	-	-	-
Self	204-707-7	124-64-1	Tetrakis(hydroxymethyl)phosphonium chloride	Intermediate Use Only	-	-	-	-	-
Self	207-096-5	434-03-7	Ethisterone	Intermediate Use Only	-	-	-	-	-
Self	207-563-3	481-29-8	3-β-hydroxy-5-α-androstan-17-one	Intermediate Use Only	-	-	-	-	-
Self	211-765-7	693-98-1	2-methylimidazole	Intermediate Use Only	-	-	-	-	-

Table X9-7: Identities of REACH registered substances with CLH or confirmed CLI self-classification for R 1A/1B but not for C or M 1a/1b									
Type	EC no.	CAS	Name	Total tonnage Band	Restr.	Auth.	Cand. list	CORAP	Indicative OEL
Self	212-686-0	846-48-0	Boldenone	Intermediate Use Only	-	-	-	-	-
Self	214-646-8	1177-87-3	Dexamethasone 21-acetate	Intermediate Use Only	-	-	-	-	-
Self	215-960-8	1461-25-2	Tetrabutyltin	Intermediate Use Only	-	-	-	-	-
Self	218-370-9	2135-17-3	Flumetasone	Intermediate Use Only	-	-	-	-	-
Self	218-612-3	2203-97-6	Hydrocortisone 21-(hydrogen succinate)	Intermediate Use Only	-	-	-	-	-
Self	220-581-6	2823-42-9	6α,9-difluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione 21-acetate	Intermediate Use Only	-	-	-	-	-
Self	220-863-9	2921-57-5	11β,17,21-trihydroxy-6α-methylpregna-1,4-diene-3,20-dione 21-(hydrogen succinate)	Intermediate Use Only	-	-	-	-	-
Self	224-585-9	4419-39-0	Beclometasone	Intermediate Use Only	-	-	-	-	-
Self	244-398-6	21462-39-5	Clindamycin hydrochloride	Intermediate Use Only	-	-	-	-	-
Self	246-119-3	24280-93-1	Mycophenolic acid	Intermediate Use Only	-	-	-	-	-
Self	252-549-2	35410-28-7	11β,17,21-trihydroxypregna-1,4-diene-3,20-dione 21-methanesulphonate	Intermediate Use Only	-	-	-	-	-
Self	259-709-0	55566-30-8	Tetrakis(hydroxymethyl)phosphonium sulphate(2:1)	Intermediate Use Only	-	-	-	-	-
Self	259-996-2	56107-04-1	3-(p-tert-butylphenyl)-2-methylpropanol	Intermediate Use Only	-	-	-	-	-
Self	263-580-6	62518-65-4	3-(m-tert-butylphenyl)-2-methylpropionaldehyde	Intermediate Use Only	-	-	-	-	-
Self	296-543-8	92731-41-4	Ethanol, 2-amino-, reaction products with ammonia, 1-piperazineethanamine fraction	Intermediate Use Only	-	-	-	-	-
Self	600-229-1	10161-33-8	17Î²-Hydroxy-estra-4,9,11-trien-3-one	Intermediate Use Only	-	-	-	-	-
Self	604-855-6	152459-95-5	Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-	Intermediate Use Only	-	-	-	-	-
Self	609-368-2	3724-43-4	Chloromethylene dimethylammonium chloride	Intermediate Use Only	-	-	-	-	-
Self	610-717-6	5173-46-6	13-methyl-1,2,6,7,8,11,12,14,15,16-decahydrocyclopenta[a]phenanthrene-3,17-dione	Intermediate Use Only	-	-	-	-	-
Self	803-261-6	198470-84-7	N-[[4-(5-methyl-3-phenylisoxazol-4-yl]phenyl]sulfonyl]propanamide	Intermediate Use Only	-	-	-	-	-
Self	808-058-6	147403-03-0	2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-biphenyl-4-yl]methyl}-1H-benz-imidazole-7-carboxylic acid	Intermediate Use Only	-	-	-	-	-

Table X9-7: Identities of REACH registered substances with CLH or confirmed CLI self-classification for R 1A/1B but not for C or M 1a/1b									
Type	**EC no.**	**CAS**	**Name**	**Total tonnage Band**	**Restr.**	**Auth.**	**Cand. list**	**CORAP**	**Indicative OEL**
Self	801-607-0	302962-49-8	N-(2-chloro-6-methylphenyl)-2-({6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-yl}amino)-1,3-thiazole-5-carboxamide	Intermediate Use Only	-	-	-	-	-
NONS - R Based on CLH - Restricted/authorised, n= 1									
CLH	401-040-5	75113-37-0	Dibutyltin hydrogen borate	No tonnage or use data	Y	-	-	-	-
NONS - R Based on CLH - Not restricted/authorised, n=13									
CLH	401-720-1	6807-17-6	2,2-bis(4'-hydroxyphenyl)-4-methylpentane	No tonnage or use data	-	-	-	-	-
CLH	401-750-5	17570-76-2	Lead(II) bis(methanesulfonate)	No tonnage or use data	-	-	Y	-	-
CLH	402-660-9	-	A mixture of: disodium 4-(3-ethoxycarbonyl-4-(5-(3-ethoxycarbonyl-5-hydroxy-1-(4-sulfonatophenyl)pyrazol-4-yl)penta-2,4-dienylidene)-4,5-dihydro-5-oxopyrazol-1-yl)benzenesulfonate; trisodium 4-(3-ethoxycarbonyl-4-(5-(3-ethoxycarbonyl-5-oxido-1-(4-sulfonatophenyl)pyrazol-4-yl)penta-2,4-dienylidene)-4,5-dihydro-5-oxopyrazol-1-yl)benzenesulfonate	No tonnage or use data	-	-	-	-	-
CLH	403-250-2	-	A mixture of: 4-[[bis-(4-fluorophenyl)methylsilyl]methyl]-4H-1,2,4-triazole; 1-[[bis-(4-fluorophenyl)methylsilyl]methyl]-1H-1,2,4-triazole	No tonnage or use data	-	-	-	-	-
CLH	405-020-7	105024-66-6	(4-ethoxyphenyl)(3-(4-fluoro-3-phenoxyphenyl)propyl)dimethylsilane	No tonnage or use data	-	-	-	-	-
CLH	406-850-2	106325-08-0, 133855-98-8	epoxiconazole (ISO)	No tonnage or use data	-	-	-	-	-
CLH	414-200-4	119738-06-6	(+/-) tetrahydrofurfuryl (R)-2-[4-(6-chloroquinoxalin-2-yloxy)phenyloxy]propionate	No tonnage or use data	-	-	-	-	-
CLH	418-260-2	183196-57-8	[containing < 0.5 % N,N-dimethylformamide (EC no 200-679-5)]	No tonnage or use data	-	-	-	-	-
CLH	420-580-2	151798-26-4	2-[2-hydroxy-3-(2-chlorophenyl)carbamoyl-1-naphthylazo]-7-[2-hydroxy-3-(3-methylphenyl)carbamoyl-1-naphthylazo]fluoren-9-one	No tonnage or use data	-	-	-	-	-
CLH	421-150-7	143860-04-2	3-ethyl-2-methyl-2-(3-methylbutyl)-1,3-oxazolidine	No tonnage or use data	-	-	Y	-	-

Table X9-7: Identities of REACH registered substances with CLH or confirmed CLI self-classification for R 1A/1B but not for C or M 1a/1b									
Type	**EC no.**	**CAS**	**Name**	**Total tonnage Band**	**Restr.**	**Auth.**	**Cand. list**	**CORAP**	**Indicative OEL**
CLH	421-960-0	90035-08-8	A mixture of: cis-4-hydroxy-3-(1,2,3,4-tetrahydro-3-(4-(4-trifluoromethylbenzyloxy)phenyl)-1-naphthyl)coumarin; trans-4-hydroxy-3-(1,2,3,4-tetrahydro-3-(4-(4-trifluoromethylbenzyloxy)phenyl)-1-naphthyl)coumarin	No tonnage or use data	-	-	-	-	-
CLH	428-010-4	82413-20-5	(E)-3-[1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-phenylbut-1-enyl]phenol	No tonnage or use data	-	-	-	-	-
CLH	435-470-1	27366-72-9	N,N-(dimethylamino)thioacetamide hydrochloride	No tonnage or use data	-	-	-	-	-

Step 5: Prioritisation

The objective of substance prioritisation has been to focus the monetisation of effects to be undertaken in the later stages of this study. Major reprotoxins (all Non C non M) from the following classification categories have been screened:

- R1 Fully Registered, CLH, Restriction or Authorisation (hereinafter 'RA');
- R1 Fully Registered, CLH, No Restriction or Authorisation (hereinafter 'no RA'); and
- R1 Fully Registered Self-classification.

These classes have been selected as there is sufficient information available.[362]

A risk ranking technique has been employed to select the list of reprotoxins to be evaluated. Thirty chemicals were prioritized using this approach. Three aprotic solvents were added at the request of the Steering Group set up for this study.

Although it could be argued that phthalates also have a similarly high profile, the study team has prioritised aprotic solvents because phthalates (DEHP, DBP, BBP, DIBP) are already regulated by bans, restrictions or authorisation in all uses other than some food contact materials and medical devices (although this may also now be restricted). Industry is thus moving away from their use due to this national level legislation. At this point, there is little (DBP for maleic anhydride but RAC agreed as below threshold and DEHP for medical devices – again below threshold) to no production in the EU of the above phthalates. An assessment would thus not yield any present exposure data and hence risk. The aprotic solvents, on the other hand, and NMP in particular, are still in widespread use.

We developed a risk ranking approach for the selection process. Since risk is commonly defined as the product of hazard and exposure, we needed to develop surrogates for both hazard and exposure. Instead of Hazard Indices we used a surrogate that was at hand and easily extracted from ECHA's databases; the DNELs. Given that DNELs are meant to represent the level below which risk is not to be measured/encountered it was appropriated as a good surrogate for health hazard.

Tonnages, as a surrogate for exposure for each of the substances, have been obtained from REACH registrations. The tonnage range has been converted to a geometric mean (one significant digit); for example, a tonnage range of 10-100 tonnes has been converted to 30 tonnes. Where no DNEL is available, a value of 1 has been used. Sensitivity analyses showed no differences in final selections, based upon our selection of a default value of 1. A risk index can then be derived.[363]

[362] For intermediate and NONS (Notification of New Substances) substances, volumes/tonnages are not available and DNEL values are not available in the majority of cases. Intermediate substances are within the scope of the study but the available data may not allow quantification.

[363] Usage of DNELs for overview, nominal risk estimates was endorsed by Eurostat, REACH Baseline study p10, https://ec.europa.eu/eurostat/documents/3888793/5844937/KS-RA-09-003-EN.PDF/351b1a93-fe8a-4085-8c67-4566fc8c6b48?version=1.0

For each classification category, substances/groups with risk contributions greater than 1% have been selected in the final list of substances. See Table X9-8.

Table X9-8: Risk based selection for reprotoxins for inclusion											
Class type	EC No	CAS No	Name	Classifica-tion	Total tonnage (tonnes per annum)	Geo-metric Tonnage (tonnes per annum)	Local DNEL	System-atic DNEL	Risk	Risk %	Selected %
R1 Fully Registered CLH RA											
CLH	201-245-8	80-05-7	4,4'-isopropylidenediphenol	R 1A/1B	1000000 - 10000000	3000000	2	2	1500000	32.89	32.89
CLH	231-100-4	7439-92-1	Lead	R 1A/1B	1000000 - 10000000	3000000	-	-	3000000	65.78	65.78
R1 Fully registered CLH no RA											
CLH	201-039-8	77-58-7	Dibutyltin dilaurate	R 1A/1B; M2	100-100	300	-	0.02	15000	5.21	5.21
CLH	201-861-7	88-85-7	Dinoseb	R 1A/1B	1000-10000	3000	-	0.04	75000	26.04	26.04
CLH	202-506-9	96-45-7	Imidazolidine-2-thione	R 1A/1B	100-1000	300	-	0.07	4286	1.49	1.49
CLH	202-696-3	98-73-7	4-tert-butylbenzoic acid	R 1A/1B	100-1000	300	-	0.067	4478	1.55	1.55
CLH	203-804-1	110-80-5	2-ethoxyethanol	R 1A/1B	100-1000	300	-	0.083	3614	1.26	1.26
CLH	206-104-4	301-04-2, 6080-56-4	Lead di(acetate)	R 1A/1B	0-10	3	-	-	3	0.00	0
CLH	211-670-0	683-18-1	Dibutyltin dichloride	R 1A/1B; M2	10-100	30	-	0.01	3000	1.04	1.04
CLH	215-125-8	1303-86-2	Diboron trioxide	R 1A/1B	1000-10000	3000	-	4.66	644	0.22	0.22
CLH	215-540-4	1303-96-4, 1330-43-4, 12179-04-3	Disodium tetraborate, anhydrous	R 1A/1B	100000 - 1000000	300000	-	6.7	44776	15.55	15.55

Table X9-8: Risk based selection for reprotoxins for inclusion											
Class type	EC No	CAS No	Name	Classifica-tion	Total tonnage (tonnes per annum)	Geo-metric Tonnage (tonnes per annum)	Local DNEL	System-atic DNEL	Risk	Risk %	Selected %
CLH	233-139-2	10043-35-3	Boric acid	R 1A/1B	100000 - 1000000	300000	-	8.3	36145	12.55	12.55
CLH	234-390-0	10332-33-9, 11138-47-9, 12040-72-1, 37244-98-7	Perboric acid, sodium salt	R 1A/1B	1000-10000	3000	-	2	15000	5.21	5.21
CLH	234-541-0	12008-41-2, 12280-03-4	Disodium octaborate	R 1A/1B	1000-10000	3000	-	6.9	435	0.15	0.15
CLH	239-622-4	15571-58-1	2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate	R 1A/1B	1000-10000	3000	-	0.062	48387	16.80	16.8
CLH	310-154-3	121158-58-5	Phenol, dodecyl-, branched	R 1A/1B	10000-100000	30000	-	-	30000	10.42	10.42
CLH	200-679-5	68-12-2	N,N-Dimethylformamide (DMF)	R 1A/1B	10000-100000	30000		15	2000	0.69	0.69
CLH	204-826-4	127-19-5	N,N-Dimethylacetamide (DMAA)	R 1A/1B	10000-100000	30000		23	1304	0.45	0.45
CLH	212-828-1	872-50-4	1-Methyl-2-pyrrolidone (NMP)	R 1A/1B	10000-100000	30000		40	750	0.26	0.26
								Total	**288096**	**100**	**97.49**
R1 Fully Registered Self											
Self	200-683-7	68-26-8	Retinol	R1A/B; R2	0-10	3	-	-	3	0.00	0
Self	201-228-5	79-81-2	Retinyl palmitate	R1A/B; R2	100-1000	300	-	-	300	0.05	0.05

Table X9-8: Risk based selection for reprotoxins for inclusion											
Class type	EC No	CAS No	Name	Classifica-tion	Total tonnage (tonnes per annum)	Geo-metric Tonnage (tonnes per annum)	Local DNEL	System-atic DNEL	Risk	Risk %	Selected %
Self	201-289-8	80-54-6	2-(4-tert-butylbenzyl)propionaldehyde	R1A/B; R2	1000-10000	3000	-	0.44; 0.201	6818	1.09	1.09
Self	212-449-1	818-08-6	Dibutyltin oxide	R1A/B; R2	1000-10000	3000	-	0.01	300000	47.84	47.84
Self	220-481-2	2781-10-4	Dibutyltin bis(2-ethylhexanoate)	R1A/B; R2	10-100	30	-	0.01	3000	0.48	0.48
Self	235-252-2	12141-20-7	Trilead dioxide phosphonate	R1A/B; R2	100000-1000000	300000	-	-	300000	47.84	47.84
Self	259-048-8	54261-67-5	Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate)	R1A/B; R2	10-100	30	-	7.3	4	0	0
Self	272-233-8	68784-25-8	Phenol, dodecyl-,sulfurized, carbonates, calcium salts	R1A/B; R2	100-1000	300	-	3.5	86	0.01	0.01
Self	272-234-3	68784-26-9	Phenol, dodecyl-,sulfurized, carbonates, calcium salts, overbased	R1A/B; R2	10000-100000	30000	-	3.5; 0.14	8571	1.37	1.37
Self	272-486-4	68855-45-8	Phenol, dodecyl-,sulfurized, calcium salts	R1A/B; R2	1000-10000	3000	-	3.5	857	0.14	0.14
Self	306-115-5	96152-43-1	Phenol, dodecyl-,branched, sulfurized	R1A/B; R2	100-1000	300	-	3.526	85	0.01	0.01
								Total	**627059**	**100**	**98014**
All these substances are fully registered under REACH and are joint submissions											

Annex 10 Lead

X10.1 Introduction

X10.1.1 Relevant substances[364]

This section focusses on the following three lead compounds:

- Lead (CAS No. 7439-92-1, EC No. 231-100-4);
- Lead di(acetate) (EC No 206-104-4; CAS No: 301-04-2, 6080-56-4); and
- Trilead dioxide phosphonate (EC No: 235-252-2; CAS No: 12141-20-7).

X10.1.2 Hazard classifications

Reproductive and non-reproductive hazard classifications for lead compounds are presented in the tables below. These include environmental hazard classifications.

Table X10-1: Lead compounds – reproductive hazard classifications

Compound	Category	Hazard code	Explanation
Lead	R1 Fully registered CLH RA R 1A/1B	H360FDH362	May damage fertility or the unborn child
		H362	May cause harm to breastfed children
Lead di(acetate)	R1 Fully registered CLH no RA R 1A/1B	H360DfH373	May damage the unborn child
Trilead dioxide phosphonate	R1 Fully Registered Self R1A/B; R2	H360	May damage fertility or the unborn child
		H361	Suspected of damaging fertility or the unborn child
		H362	May cause harm to breastfed children

Sources:
ECHA, Substance information, lead, accessed at: https://echa.europa.eu/substance-information/-/substanceinfo/100.028.273 on 21 November 2018.
ECHA, Substance information, trilead dioxide phosphate, accessed at: https://echa.europa.eu/substance-information/-/substanceinfo/100.032.035 on 21 November 2018.
ECHA, Substance information, Lead di(acetate), accessed at: https://echa.europa.eu/brief-profile/-/briefprofile/100.005.551 on 21 November 2018

[364] http://www.commonchemistry.org/ChemicalDetail.aspx?ref=80-05-7

Table X10-2: Lead compounds – non-reproductive hazard classifications		
Compound	**Hazard code**	**Explanation**
Lead	H302	Harmful if swallowed
	H332	Harmful if inhaled
	H341	Suspected of causing genetic defects
	H351	Suspected of causing cancer
	H372	Causes damage to organs through prolonged or repeated exposure
	H373	May cause damage to organs through prolonged or repeated exposure
	H400	Very toxic to aquatic life
	H401	May cause long lasting harmful effects to aquatic life
Lead di(acetate)	H373	May cause damage to organs through prolonged or repeated exposure
	H400H410	Very toxic to aquatic life
	H410	Very toxic to aquatic life with long lasting effects
Trilead dioxide phosphonate	H228	Flammable solid
	H351	Suspected of causing cancer
	H372	Causes damage to organs through prolonged or repeated exposure
	H373	May cause damage to organs through prolonged or repeated exposure
	H400	Very toxic to aquatic life
	H332	Harmful if inhaled
	H302	Harmful if swallowed
	H410	Very toxic to aquatic life with long lasting effects
Sources: *ECHA, Substance information, lead, accessed at: https://echa.europa.eu/substance-information/-/substanceinfo/100.028.273 on 21 November 2018.* *ECHA, Substance information, trilead dioxide phosphate, accessed at: https://echa.europa.eu/substance-information/-/substanceinfo/100.032.035 on 21 November 2018.* *ECHA, Substance information, Lead di(acetate), accessed at: https://echa.europa.eu/brief-profile/-/briefprofile/100.005.551 on 21 November 2018*		

X10.1.3 Existing OELs and BLVs

The European Commission has set a binding OEL of 150 µg lead/m^3 calculated over a 40-hour working week, and a binding BLV of 70 µg lead/dL[365]. Many EU countries have in place lower BLVs.

The OELs and BLVs in EU Member States are summarised below.

Table X10-3: OELs and BLVs for lead in the EU		
Country	**OEL 8-hr TWA**	**BLV**
Austria	0.1 mg/m^3	70 µg Pb/100 ml in blood (men, women >50 years) 45 µg Pb/100 ml in blood (women <50 years)
Belgium	0.15 mg/m^3	70µg/100ml
Bulgaria	0.05 mg/m^3	400 µg/l and 300µg/l (women <45 years old)
Croatia	0.15 mg/m^3	70µg/100ml
Cyprus		70µg/100ml

[365] State of the art report on reproductive toxicants European Agency for Safety and Health at Work accessed at: https://publications.europa.eu/en/publication-detail/-/publication/732d46bf-e45c-11e6-ad7c-01aa75ed71a1/language-en on 10 August 2018.

Table X10-3: OELs and BLVs for lead in the EU		
Country	**OEL 8-hr TWA**	**BLV**
Czech Republic	0.05 mg/m^3	400 µg/l
Denmark	0.05 mg/m^3	20µg Pb/100 ml blood
Estonia	0.1 mg/m^3	None identified (actions to be taken vary according to previous measured concentrations)
Finland	0.1 mg/m^3	50µg/dl (male) 40 µg/dl (female)
France	0.1 mg/m^3	400µg/l (male) and 300µg/l (female)
Germany	0.15 mg/m^3	400µg /l (men and women >45 years old) 300 µg/l (women <45 years old)
Greece	0.15 mg/m^3	70µg/100ml
Hungary	0.15 mg/m^3	400µg /l and 300 µg/l for women <45 years old
Ireland	0.15 mg/m^3	70µg/100ml
Italy	0.1 mg/m^3	60µg/100 ml 40µg/100 ml (women of childbearing age)
Latvia	0.005 mg/m^3	40µg/100ml
Lithuania	0.15 mg/m^3	70µg/100ml
Luxembourg	0.15 mg/m^3	70µg/100ml
Malta	0.15 mg/m^3	70µg/100ml
Netherlands	0.15 mg/m^3	70µg/100ml
Poland	0.05 mg/m^3	50µg/100ml
Portugal	0.15 mg/m^3	70µg/100ml
Romania	0.15 mg/m^3	40µg/100ml
Slovakia	0.15 mg/m^3	400µg/l 100µg/l (women <45 years old)
Slovenia	0.1 mg/m^3	400µg/l (men) 300µg/l (women <45 years old)
Spain	0.15 mg/m^3	70µg/100ml (health surveillance is mandatory for workers when blood lead level is >40µg/100ml. The exposure of pregnant workers to lead compounds that may be absorbed by the human body is banned)
Sweden	0.1 mg/m^3	<1.5µmol/l (men and women >50 years old) <0.8 µmol/l (women <50 years old)
United Kingdom	0.15 mg/m^3	60µg/100ml (men) 30µg/100ml (women)
EU	0.15 mg/m^3	70µg/100ml
Sources: *DGUV Gestis, http://limitvalue.ifa.dguv.de/, Verisk 3E Insight for Chemicals, accessed on 10 August 2018*		

X10.1.4 Legislation other than the OSH directives

This section summarises recent legislation that has impacted on the use of lead and its compounds or has the potential to do so in the future. Only legislation other than the OSH directives that are the focus of this study is considered.

As of November 2018, the Candidate List of Substances of Very High Concern for Authorisation contains metallic lead and 31 lead compounds, including the two compounds prioritised for analysis under this study:

- Lead di(acetate); and
- Trilead dioxide phosphonate.

Both lead metal and the two relevant substances have been included on the Candidate List due to their reproductive toxicity[366]. Lead metal was added to the Candidate List in June 2018[367].

According to the RMOA for lead (Swedish Chemical Agency, 2017)[368], the following legislation/restrictions applies to lead:

- Since lead is R1A, it is covered by entry 30 in Annex XVII of REACH. This means that it cannot be placed on the market for sale to the general public.
- Lead is listed under entry number 63 in Annex XVII of REACH, which restricts lead in jewellery and in articles supplied to the general public that can be placed in the mouth by children.
- Lead and lead compounds are also covered by other pieces of EU legislation, such as the RoHS Directive, Cosmetic Regulation, Toy Safety Directive, Batteries Directive, and Pregnant Workers Directive, etc.

The following restrictions[369] are in place for lead (CAS No. 7439-92-1, EC No. 231-100-4) and its compounds in:

- Jewellery articles (weight criteria and derogations apply); and
- Articles supplied to the general public that can be placed in the mouth by children (concentration criteria and derogations apply).

Trilead dioxide phosphonate is listed in the RMOA for lead stabilisers (Denmark, 2014)[370] as one of the most common lead stabilisers. A restriction on the use of lead compounds to stabilise PVC and on the placing on the market of PVC articles stabilised with lead compounds has been proposed and evaluated by RAC and SEAC and it is currently awaiting a decision by the European Commission[371]. The European Stabiliser Producers Association (ESPA) substituted lead stabilisers in the EU by 2015 as part of the VinylPlus Voluntary Commitment[372]. However, as noted later in this document, there is still some occupational exposure in the sector 'lead oxide/stabiliser' production.

A similar proposal to restrict the use of lead and its compounds in shot (containing lead in concentrations greater than 1% by weight) for shooting with a shot gun within a wetland or where spent gunshot would land within a wetland, including shooting ranges or shooting grounds in wetlands

[366] ECHA, Candidate List of substances of very high concern for Authorisation, accessed at: https://echa.europa.eu/candidate-list-table on 21 November 2018.

[367] ECHA, 10 new substances added to the Candidate List, accessed at: https://echa.europa.eu/fi/-/ten-new-substances-added-to-the-candidate-list on 21 November 2018.

[368] Swedish Chemicals Agency (2017): Risk management option analysis conclusion document, lead, accessed at: https://echa.europa.eu/documents/10162/15058241-d9bd-264b-7c41-dd716e8f521a on 21 November 2018.

[369] ECHA, Annex XVII to REACH – Conditions of restriction, Entry 63, Lead, accessed at: https://echa.europa.eu/documents/10162/3f17befa-d554-4825-b9d5-abe853c2fda2 on 21 November 2018.

[370] ECHA (2015): Risk management option analysis conclusion document, lead stabilisers used in PVC, accessed at: https://echa.europa.eu/documents/10162/a34ce626-7f20-4d9f-819b-7eec62dd362e on 21 November 2018.

[371] ECHA, Adopted opinions on restriction proposals, Lead compounds-PVC, accessed at: https://echa.europa.eu/previous-consultations-on-restriction-proposals/-/substance-rev/16119/term on 21 November 2018.

[372] ESPA (2016): Stabilisers – What's new? Update January 2016, accessed at: https://www.stabilisers.eu/wp-content/uploads/2016/01/ESPA-stabilisers_update_January-20161.pdf on 21 November 2018.

has also been evaluated by RAC and SEAC and is currently awaiting a decision by the European Commission[373].

Lead compounds (lead carbonates and sulfates) were in the past used in paints but this use is banned (entries 16 and 17 of REACH Annex XVII), although Member States are allowed to permit the use of lead paints for restoration work[374].

Legislation that is relevant to the design, use and end of life lead batteries includes the Battery Directive, End of Life Vehicle Directive, and the Waste Framework Directive and Waste Shipment Regulations (Eurobat, 2018)[375].

X10.2 Summary of health endpoints, thresholds & DRRs

X10.2.1 Relevant health endpoints

Relevant reproductive health endpoints

The reproductive effects identified through literature review are summarised below. The table below only lists adverse effects which have a potential for human effects correlation and for which a no-effect threshold and a Dose-Response Relationship (DRR) has been derived.

Table X10-4: Lead – summary of health effects for which thresholds/dose-response data have been identified in published literature

Health effect	Fertility/ development?		Monetisable effect correlate
	Fer	Dev	
Increased Odds ratio for spontaneous abortion[376]	N/A		Spontaneous abortion or still birth
Increased pup mortality (dead pups number)	Fer		Spontaneous abortion or still birth
Increased incidence of reduced number of litters up to PND 23	Fer		Spontaneous abortion or still birth
Increased incidence of stillbirth	Fer		Spontaneous abortion or still birth
Increased frequency of preterm births[377]		Dev	Low birth weight
Decreased birth weight[378]		Dev	Low birth weight
Reduced foetus weight at birth		Dev	Low birth weight
Decreased birth weight of foetus-male		Dev	Low birth weight

[373] ECHA, Adopted opinions on restriction proposals, Lead compounds-shot, accessed at: https://echa.europa.eu/previous-consultations-on-restriction-proposals/-/substance-rev/17005/term on 21 November 2018.

[374] UK REACH Competent Authority, Information leaflet number 20 – restrictions, REACH – restrictions, accessed at: http://www.hse.gov.uk/reach/resources/20restrictions.pdf on 21 November 2018.

[375] EUROBAT, EUROBAT Position - Annex XV SVHC report published in the context of SVHC identification in accordance with REACH Article 57 – Lead, accessed at: http://www.eurobat.org/images/news/position-papers/23042018_EUROBAT_Position_Paper_on_Annex_XV_Report_on_Lead_Metal.pdf on 21 November 2018.

[376] Borja-Aburto VH, Hertz-Picciotto I, Lopez MR, et al. 1999. Blood lead levels measured prospectively and risk of spontaneous abortion. Am J Epidemiol 150:590-597.

[377] Torres-Sánchez LE, Berkowitz G, Lopez-Carrillo L, et al. 1999. Intrauterine lead exposure and preterm birth. Environ Res 81:297-301.

[378] Zhu M, Fitzgerald EF, Gelberg KH, Lin S, Druschel C. 2010. Maternal Low-Level Lead Exposure and Fetal Growth. Environ Health Perspect 118(10): 1471-1475.

Table X10-4: Lead – summary of health effects for which thresholds/dose-response data have been identified in published literature			
Health effect	**Fertility/ development?**		**Monetisable effect correlate**
	Fer	**Dev**	
Decreased birth weight of foetus-female		Dev	Low birth weight
Reduced foetus weight on postnatal day 23-male		Dev	No monetisable effect correlate
Reduced foetus weight on postnatal day 23-female		Dev	No monetisable effect correlate
Decreased pup body weight at age 5 day		Dev	No monetisable effect correlate
Decreased offspring body weight at weaning-male		Dev	No monetisable effect correlate
Decreased offspring body weight at weaning-female		Dev	No monetisable effect correlate
Decreased offspring body weight at puberty-male		Dev	No monetisable effect correlate
Decreased offspring body weight at puberty-female		Dev	No monetisable effect correlate
Decreased offspring body weight at post puberty-male		Dev	No monetisable effect correlate
Decreased offspring body weight at post puberty-female		Dev	No monetisable effect correlate
Decreased crown-to-rump length (CRL) -female		Dev	Reduced foetal growth
Decreased crown-to-rump length (CRL) -male		Dev	Reduced foetal growth
Delay in puberty with increased age at menarche[379]		Dev	No monetisable effect correlate
Reduction in 6-month head circumference at delivery (maternal BLL 1-35 µg/dl[380])		Dev	No monetisable effect correlate
Decreased anogenital distance (AGD)-male		Dev	No monetisable effect correlate
Decreased anogenital distance (AGD)-female		Dev	No monetisable effect correlate
Decreased AGD/CRL ratio-male		Dev	No monetisable effect correlate
Decreased AGD/CRL ratio-female		Dev	No monetisable effect correlate
Increased incidence of delayed vaginal opening (F1)		Dev	No monetisable effect correlate
Reduction in fertility[381]	Fer		Impaired fertility – male
Reduction in median sperm concentration[382]	Fer		Impaired fertility - male
Decreased sperm count[383]	Fer		Impaired fertility - male
Decreased Gross Sperm motility[383]	Fer		Impaired fertility - male
Increased sperm liquefaction time[383]	Fer		Impaired fertility - male

[379] Selevan SG, Rice DC, Hogan KA, Euling SY, Pfahles-Hutchens A, Bethel J. Blood lead concentration and delayed puberty in girls. New England journal of medicine. 2003 Apr 17;348(16):1527-36.

[380] Rothenberg SJ, Schnaas L, Perroni E, Hernandez RM, Martinez S, Hernandez C. 1999. Pre- and postnatal lead effect on head circumference: a case for critical periods. Neurotoxicol Teratol 21(1): 1-11.

[381] Gennart J-P, Buchet J-P, Roels H, et al. 1992b. Fertility of male workers exposed to cadmium, lead or manganese. Am J Epidemiol 135:1208-1219.

[382] Bonde JP, Joffe M, Apostoli P, Dale A, Kiss P, Spano M et al. (2002). Sperm Count and Chromatin Structure in Men Exposed to Inorganic Lead: Lowest Adverse Effect Levels. Occup Environ Med 569:234-242.

[383] Naha NI, Bhar RB, Mukherjee A, Chowdhury AR. Structural alteration of spermatozoa in the persons employed in lead acid battery factory. Indian journal of physiology and pharmacology. 2005 Apr;49(2):153. Also in http://www.niohenvis.nic.in/bibliography/Lead Health.pdf pp32-33

Table X10-4: Lead – summary of health effects for which thresholds/dose-response data have been identified in published literature			
Health effect	**Fertility/ development?**		**Monetisable effect correlate**
	Fer	**Dev**	
Lower sperm counts[384,385]	Fer		Impaired fertility - male
Decreased sperm concentration	Fer		Impaired fertility - male
Decreased total sperm count	Fer		Impaired fertility - male
Impaired male fertility	Fer		Impaired fertility - male
Reduced circulating concentration of progesterone*	Fer		Impaired fertility - female
Reduced number of foetuses/dam	Fer		Impaired fertility - female
Reduced number of implantation sites/dam	Fer		Impaired fertility - female
Increased incidence of disrupted oestrous cycle (F1)		Dev	Impaired fertility - female
Pre-eclampsia[386]	Fer		Pre-eclampsia (additional incidence)
IQ loss[387,388]		Dev	IQ loss in children (IQ points lost per child)
Inverse associations between the maternal blood lead levels and the Neonatal behavioural neurological assessment scores[389]		Dev	Impaired cognitive development – IQ Developmental neuro-impairment
Notes: *Fertility effects on F1 are treated as 'developmental' in this table. All effects observed in multiple generations are assigned to the earliest generation, e.g. F2 and F3 assigned to F1 for monetisation purposes, using the probabilities for F3 as the worst-case scenario. Effects observed in F0 and F1 are assigned to both F0 and F1, using the F1 probabilities for both F0 and F1 as the worst-case scenario.* *Shaded cells denote endpoints identified from toxicological studies. Other end points are from epidemiological studies or meta-analyses.* **Only male offspring fertility monetary value has been identified thus all cases of F1 infertility are therefore valued as male infertility.*			

X10.2.2 Summary of thresholds and DRRs

The no effect thresholds (inhalation 8-hr TWA mg/m3) and effect slopes, together with the maximum air exposure concentrations (8-hr TWA mg/m3) for which the effect slopes are valid, are summarised

[384] Assennato G et al. (1987). Sperm Count Suppression without Endocrine Dysfunction in Lead Exposed Men. Arch Environ Health 42: 124-127.

[385] NTP Monograph on Health Effects of Low-Level Lead, June 13, 2012, Department of Health and Human Services, accessed at: https://ntp.niehs.nih.gov/ntp/ohat/lead/final/monographhealtheffectslowlevellead_newissn_508.pdf on 21 November 2018.

[386] Poropat AE et al. (2018): Blood lead and preeclampsia: a meta-analysis and review of implications, Environmental Research 160 (2018): 12-19.

[387] Lanphear BP et al. (2005): Low-level environmental lead exposure and children's intellectual function: an international pooled analysis, Environmental Health Perspectives. 2005 July:113(7): 894-899.

[388] Note that child blood lead level is assumed to be 90% of maternal blood lead level as per EFSA (2010): Scientific opinion on lead in food, EFSA panel on contaminants in the food chain (CONTAM), EFSA Journal 2010, 8(4): 1570, with update published on 22 March 2013.

[389] Liu J et al., Lead exposure at each stage of pregnancy and neurobehavioral development of neonates, Neurotoxicology. 2014 Sep;44:1-7. doi: 10.1016/j.neuro.2014.03.003. Epub 2014 Apr 2 Abstract.

below. For a more detailed overview of the methods used to derive these values, please consult the methodology annex.

Table X10-5: Lead – effects, thresholds and DRRs				
Health effect	**Threshold BLL (µg/dL)**	**Slope (%/µg/dL)**	**Maximum value of slope applicability BLL (µg/dL)**	**Monetisable effect correlate**
Increased Odds ratio for spontaneous abortion[390]	5.00	13	Could not be derived	Spontaneous abortion or still birth
Increased pup mortality (dead pups number)	>30.0	24.2	462	Spontaneous abortion or still birth
Increased incidence of reduced number of litters up to PND 23	>30.0	33.7	390	Spontaneous abortion or still birth
Increased incidence of stillbirth	>30.0	2.83	786	Spontaneous abortion or still birth
Increased frequency of preterm births[391]	0.98	34.12	9.77	Low birth weight
Decreased birth weight[392]	0.50	-0.41	5	Low birth weight
Reduced foetus weight at birth	>30.0	-0.38	390	Low birth weight
Decreased birth weight of foetus-male	>30.0	-0.26	170	Low birth weight
Decreased birth weight of foetus-female	>30.0	-0.68	450	Low birth weight
Reduced foetus weight on postnatal day 23-male	>30.0	-0.10	390	No monetisable effect correlate
Reduced foetus weight on postnatal day 23-female	>30.0	-0.43	390	No monetisable effect correlate
Decreased pup body weight at age 5 day	>30.0	-0.90	462	No monetisable effect correlate
Decreased offspring body weight at weaning-male	>30.0	-0.98	462	No monetisable effect correlate
Decreased offspring body weight at weaning-female	>30.0	-0.89	462	No monetisable effect correlate
Decreased offspring body weight at puberty-male	>30.0	-0.87	462	No monetisable effect correlate
Decreased offspring body weight at puberty-female	>30.0	-0.57	462	No monetisable effect correlate
Decreased offspring body weight at post puberty-male	>30.0	-0.69	462	No monetisable effect correlate
Decreased offspring body weight at post puberty-female	>30.0	-0.33	462	No monetisable effect correlate
Decreased crown-to-rump length (CRL) -male	>30.0	-0.20	170	Reduced foetal growth

[390] Borja-Aburto VH, Hertz-Picciotto I, Lopez MR, et al. 1999. Blood lead levels measured prospectively and risk of spontaneous abortion. Am J Epidemiol 150:590-597.

[391] Torres-Sánchez LE, Berkowitz G, Lopez-Carrillo L, et al. 1999. Intrauterine lead exposure and preterm birth. Environ Res 81:297-301.

[392] Zhu M, Fitzgerald EF, Gelberg KH, Lin S, Druschel C. 2010. Maternal Low-Level Lead Exposure and Fetal Growth. Environ Health Perspect 118(10): 1471-1475.

Table X10-5: Lead – effects, thresholds and DRRs				
Health effect	**Threshold BLL (µg/dL)**	**Slope (%/µg/dL)**	**Maximum value of slope applicability BLL (µg/dL)**	**Monetisable effect correlate**
Decreased crown-to-rump length (CRL) -female	>30.0	-0.24	450	Reduced foetal growth
Delay in puberty with increased age at menarche[393]	>1	1.2	4	No monetisable effect correlate
Reduction in 6-month head circumference at delivery maternal BLL 1-35 µg/dl[394]	2	-0.98	7	No monetisable effect correlate
Decreased anogenital distance (AGD)-male	>30.0	-0.40	170	No monetisable effect correlate
Decreased anogenital distance (AGD)-female	>30.0	-0.19	170	No monetisable effect correlate
Decreased AGD/CRL ratio-male	>30.0	-0.21	170	No monetisable effect correlate
Decreased AGD/CRL ratio-female	>30.0	-0.05	170	No monetisable effect correlate
Increased incidence of delayed vaginal opening (F1)	>30.0	0.99	462	No monetisable effect correlate
Reduction in fertility [395]	4.63	-1.56	46.3	Impaired fertility - male
Reduction in median sperm concentration[396]	44 (40)	5.8	Could not be derived	Impaired fertility - male
Decreased sperm count[397]	>7	-3.1	35?	Impaired fertility - male
Decreased Gross Sperm motility[397]	>7	-2.1	35?	Impaired fertility - male
Increased sperm liquefaction time[397]	>7	4.4	35?	Impaired fertility - male
Lower sperm counts[398,399]	18	-0.70	79	Impaired fertility - male
Decreased sperm concentration[399]	19.2	-0.77	66.5	Impaired fertility - male
Decreased total sperm count[399]	19.2	-1.49	66.5	Impaired fertility - male

[393] Selevan SG, Rice DC, Hogan KA, Euling SY, Pfahles-Hutchens A, Bethel J. Blood lead concentration and delayed puberty in girls. New England journal of medicine. 2003 Apr 17;348(16):1527-36.

[394] Rothenberg SJ, Schnaas L, Perroni E, Hernandez RM, Martinez S, Hernandez C. 1999. Pre- and postnatal lead effect on head circumference: a case for critical periods. Neurotoxicol Teratol 21(1): 1-11.

[395] Gennart J-P, Buchet J-P, Roels H, et al. 1992b. Fertility of male workers exposed to cadmium, lead or manganese. Am J Epidemiol 135:1208-1219.

[396] Bonde JP, Joffe M, Apostoli P, Dale A, Kiss P, Spano M et al. (2002). Sperm Count and Chromatin Structure in Men Exposed to Inorganic Lead: Lowest Adverse Effect Levels. Occup Environ Med 569:234-242.

[397] Naha NI, Bhar RB, Mukherjee A, Chowdhury AR. Structural alteration of spermatozoa in the persons employed in lead acid battery factory. Indian journal of physiology and pharmacology. 2005 Apr;49(2):153. Also in http://www.niohenvis.nic.in/bibliography/Lead Health.pdf pp32-33

[398] Assennato G et al. (1987). Sperm Count Suppression without Endocrine Dysfunction in Lead Exposed Men. Arch Environ Health 42: 124-127.

[399] NTP Monograph on Health Effects of Low-Level Lead, June 13, 2012, Department of Health and Human Services, accessed at: https://ntp.niehs.nih.gov/ntp/ohat/lead/final/monographhealtheffectslowlevellead_newissn_508.pdf on 21 November 2018.

Table X10-5: Lead – effects, thresholds and DRRs				
Health effect	**Threshold BLL (µg/dL)**	**Slope (%/µg/dL)**	**Maximum value of slope applicability BLL (µg/dL)**	**Monetisable effect correlate**
Impaired male fertility[400]	25	0.002	60	Impaired fertility - male
Reduced circulating concentration of progesterone	70.0	-0.52	87	Impaired fertility - female
Reduced number of foetuses/dam	>30.0	-0.77	390	Impaired fertility - female
Reduced number of implantation sites/dam	>30.0	-0.62	390	Impaired fertility - female
Increased incidence of disrupted oestrous cycle (F1)	>30.0	2.97	462	Impaired fertility - female
Pre-eclampsia[401]	5	0.016	15	Pre-eclampsia (additional incidence)
IQ loss[402,403]	5 (1.7)	0.14	40	IQ loss in children (IQ points lost per child)
Inverse associations between the maternal blood lead levels and the Neonatal behavioural neurological assessment scores[404]	5	Could not be derived	Could not be derived	Impaired cognitive development – IQ Developmental neuro-impairment
Notes: *Shaded cells denote endpoints identified from toxicological studies. Other end points are from epidemiological studies or meta-analyses*				

X10.3 Relevant sectors, uses, and operations

The production rate of lead and its inorganic compounds in the EU is in excess of 10 million tonnes per year. Occupational exposure of workers happens primarily in industries that produce or recycle lead, or consume large quantities of lead or lead compounds (such as lead battery production). Exposure also occurs in the ceramics and lead crystal glass sectors and PVC processing[405].

[400] Estimated dose response relationship based on relative risk data from Sallmén M et al. (2000): Paternal exposure to lead and infertility, Epidemiology, 11, 148-152 and background male infertility risk in Europe from Argaval et al. (2015): A unique view on male infertility around the globe, Reproductive Biology and Endocrinology, 13, 37.

[401] Poropat AE et al. (2018): Blood lead and preeclampsia: a meta-analysis and review of implications, Environmental Research 160 (2018): 12-19.

[402] Lanphear BP et al. (2005): Low-level environmental lead exposure and children's intellectual function: an international pooled analysis, Environmental Health Perspectives. 2005 July:113(7): 894-899.

[403] Note that child blood lead level is assumed to be 90% of maternal blood lead level as per EFSA (2010): Scientific opinion on lead in food, EFSA panel on contaminants in the food chain (CONTAM), EFSA Journal 2010, 8(4): 1570, with update published on 22 March 2013.

[404] Liu J et al., Lead exposure at each stage of pregnancy and neurobehavioral development of neonates, Neurotoxicology. 2014 Sep; 44:1-7. doi: 10.1016/j.neuro.2014.03.003. Epub 2014 Apr 2 Abstract

[405] SUBSPORT Specific Substances Alternatives Assessment – Lead and its inorganic compounds, March 2013 accessed at https://www.subsport.eu/wp-content/uploads/data/lead.pdf on 21 November 2018.

Lead is registered in the tonnage band 1,000,000 – 10,000,000 tonnes per annum. Its registered uses are:

- Lead battery production
- Lead sheet production
- Use of lead metal in the production of a range of lead articles (e.g. cast, rolled and extruded products, ammunition, lead shot)
- Use of lead metal in the production of leaded steels
- Lead powder production
- Use of lead metal in lead oxide production and use of lead oxide in stabiliser production

According to IARC, uses of lead in descending order of predominance are the following: batteries; pigments and other compounds; rolled and extruded products; alloys; shot/ ammunition; cable sheathing; gasoline additives (IARC, 2006). Lead metal is mainly used in lead - acid batteries, which are used in vehicles, and in emergency systems (e.g. hospitals) as well as in industrial batteries found in computers and fork lift trucks. Lead metal is further used in sheet form in the building trade, as shot for alloying and ammunition, in soldering alloys, cable sheathing, and for the production of oxides, pigments, stabilisers and other lead compounds.

Potentially relevant sectors identified from literature review are listed in the following table. Those which have ceased or are expected to cease to be relevant due to legal and market developments are highlighted in red. The sectors which are expected to be most relevant are indicated in green, with the remaining sectors highlighted in amber.

Table X10-6: Lead – sectors and uses		
Sector	**Uses and/or activities**	**Notes (NACE codes, etc.)**
Lead battery production	Use in automobile starting, lighting and ignition (SLI) batteries; emergency lighting; traction (propulsion) batteries	C20: Manufacture of chemicals and chemical products
Lead battery recycling	Separation of the component parts of batteries; smelting and refining of the lead components	
Primary lead production	Production of metallic lead from lead ore concentrates for use in metals	C20: Manufacture of chemicals and chemical products C20.51: Manufacture of explosives C25: Manufacture of fabricated metal products, except machinery and equipment C26: Manufacture of computer, electronic and optical products C27: Manufacture of electrical equipment

Table X10-6: Lead – sectors and uses		
Sector	**Uses and/or activities**	**Notes (NACE codes, etc.)**
Secondary lead production	Production of refined metal by processing lead scrap via re-melting or smelting, refining, alloying and casting	C20: Manufacture of chemicals and chemical products C20.51: Manufacture of explosives C25: Manufacture of fabricated metal products, except machinery and equipment C26: Manufacture of computer, electronic and optical products C27: Manufacture of electrical equipment C29: Manufacture of motor vehicles, trailers and semi-trailers G: Wholesale and Retail Trade; Repair of Motor Vehicles and Motorcycles
Lead sheet production	Production of rolled and extruded products for use in machinery and vehicles; radiation shielding; roofing and flashing; soundproofing	C25: Manufacture of fabricated metal products, except machinery and equipment C29: Manufacture of motor vehicles, trailers and semi-trailers G: Wholesale and Retail Trade; Repair of Motor Vehicles and Motorcycles
Ceramic ware production	Use in ceramic glazes predominantly on earthenware; potteries, glazers and transfers	C20: Manufacture of chemicals and chemical products
Lead crystal glass production	Production of decorative glass; cutting and etching	C20: Manufacture of chemicals and chemical products
Glass recycling	Including TV or computer monitors containing cathode ray tubes (CRT)	
Lead oxide and stabiliser production	Intermediates in the manufacture of lead special glass and lead crystal glass	C20: Manufacture of chemicals and chemical products
Shipbuilding, repairing and breaking	Use in tank lining, corrosion protection	
Manufacture of computer, electronic and optical products, electrical equipment	Prevention of primary moisture ingress, use in underground applications	C22.1: Manufacture of rubber products C26: Manufacture of computer, electronic and optical products C27: Manufacture of electrical equipment
Demolition industry	Hot cutting in demolition and dismantling operations	
Ammunition	Production of shot	C20.51: Manufacture of explosives
Jewellery making and enamelling	Casting/extrusion; badge and jewellery enamelling and other vitreous enamelling	
Heat stabilisers in PVC and elastomers	Use of lead oxide for heat stabilisation	C22.2: Manufacture of plastic products
Manufacture of pigments and colours	Restoration paints, traffic paints	C20.3: Manufacture of paints, varnishes and similar coatings, printing inks and mastics
Work with metallic lead and lead containing alloys	Solder used in electrical and electronic industries	

Table X10-6: Lead – sectors and uses		
Sector	**Uses and/or activities**	**Notes (NACE codes, etc.)**
Painting of buildings and vehicles	Use of lead paints and coatings on steel structures, road markings, and in consumer products (e.g. spray-painting of automobiles)	
Paint removal	Blast removal and burning of old lead paint; stripping of old lead paint from doors, windows etc	
Manufacture of inorganic or organic lead compounds	Including lead salts, fatty acids	
Scrap industry (including pipes, flashing, cables)	Separation of component parts which may include lead	
Sources: *ECHA Substance information – lead, accessed at https://echa.europa.eu/substance-information/-/substanceinfo/100.028.273 on 15th August 2018* *SUBSPORT Specific Substances Alternatives Assessment – Lead and its inorganic compounds, accessed at https://www.subsport.eu/wp-content/uploads/data/lead.pdf on 15th August 2018* *HSE, Exposure to Lead in Great Britain 2016, accessed at http://www.hse.gov.uk/statistics/causdis/lead/lead.pdf on 15th August 2018* *HSE, 2012, Lead and you accessed at http://www.hse.gov.uk/pubns/indg305.pdf on 15th August 2018* *International Lead Association*		

Occupational exposure of workers happens primarily in industries that produce or recycle lead, or consume large quantities of lead or lead compounds (such as battery production). Exposure also occurs in the ceramics and lead crystal glass sectors and PVC processing[406].

X10.4 Exposed workforce

A number of sources provide data on occupational exposure to lead and lead compounds. In order to focus the study on sectors that continue to be relevant and have a potential for exposure above the thresholds for reprotoxic effects, this report gives preference to more recent reports that also provide data on the extent of exposure. In addition, sources which have a broad focus and provide data for all lead compounds more generally have not been used for modelling under this study.

X10.4.1 SUMER

The two key sources that have been considered but are not used for estimations in this study are CAREX and the Medical Monitoring Survey of Professional Risks (Surveillance médicale des expositions aux risques professionnels, SUMER). These data are extrapolations from a sample of workers who self-declare exposure in a survey administered by company medical officers during the workers' regular compulsory medical examination[407]. For example, the data reported by an earlier SUMER

[406] SUBSPORT Specific Substances Alternatives Assessment – Lead and its inorganic compounds, March 2013 accessed at https://www.subsport.eu/wp-content/uploads/data/lead.pdf on 21 November 2018.

[407] Eurofound (2013): France: Working conditions and occupational risks: SUMER 2010, accessed at: https://www.eurofound.europa.eu/observatories/eurwork/articles/working-conditions/france-working-conditions-and-occupational-risks-sumer-2010 on 21 November 2018.

survey for 2003 were extrapolated from a sample of 379 workers who declared that they may have been exposed to lead and its compounds[408].

Table X10-7: Workers exposed to lead and its compounds in the SUMER survey (2010)	
Total no. of workers (% of the workforce)	115,300 (0.5%)
Duration of exposure (hours per WEEK)	No indication: 5,600 (4.8%) <2h 65,700 (57%) 2-10h 22,000 (19.1%) 10-20h 7,300 (6.4%) >20h 14,700 (12.7%)
Extent of exposure	Not declared: 17,300 (15%) Very low: 67,900 (58.9%) Low: 22,600 (19.6%) High: 5,300 (4.6%) Very high: N/A
Note: Low exposure: less than 50% of OEL, High exposure: >50% of OEL, Very high exposure: may exceed OEL. *Source: SUMER report for 2010, accessed at: http://dares.travail-emploi.gouv.fr/IMG/pdf/synthese_stat_no_13_-_les_expositions_aux_produits_chimiques.pdf on 21 Nov 2018*	

It should be noted that the SUMER estimates are based on self-declaration and encompass a large number of workers that are exposed to low concentrations for short periods of time (in the 2010 dataset, the majority of workers are exposed to 'very low' concentrations for less than 2 hours per week). As noted in the explanatory note for the SUMER 2003 survey, the respondents were considered exposed as soon as the agent was present at the workplace, regardless of the duration and intensity of exposure. As a result, workers in the SUMER dataset should be treated as 'potentially exposed' rather than exposed to specific concentrations, in particular since the exposure levels are extrapolated from a limited set of self-estimated values.

In addition, the SUMER data consider all lead compounds and sectors that may have since reduced or eliminated exposure to lead.

X10.4.2 Lead REACH Consortium

The exposed workforce is summarised below. A survey of blood lead levels (BLL) is carried out by the Lead REACH Consortium every four years or thereabouts. Companies in the lead production and use sectors report data on individual blood lead measurements per worker (anonymised) to the International Lead Association (ILA) Secretariat. A statistical analysis (min, max, mean, average, P75 and P90) of these data from the 2013-16 blood lead survey by the Consortium have been provided to the consultants within the framework of this study. These data were also submitted to ECHA in August 2018 within the framework of an update of the lead metal dossier[409]. Although these data are for individual measurements, they allow the estimation of the numbers of workers under medical surveillance; it is estimated that, on average, each worker provides four samples for each survey.

[408] Institut de Veille Sanitaire, Sumex 2, Réalisation d'une matrice emplois-expositions à partir des données de l'enquête Sumer 2003, accessed at: http://www.ladocumentationfrancaise.fr/var/storage/rapports-publics/074000542.pdf on 21 November 2018.

[409] Lead REACH Consortium, accessed at: https://ila-reach.org/consortium-activities/registration/ on 21 November 2018.

Table X10-8: Exposed workforce – REACH Lead Consortium 2013-16 survey				
Sector	Total	Men	Women	
			All female workers	Female workers of reproductive age (<46 years)
Lead battery production	11,000	10,500	470	200
Primary lead production	2,500	2,450	60	50
Secondary lead production	3,000	2,870	130	90
Lead sheet production	350	340	10	< 5
Ceramic ware production	350	330	30	25
Lead crystal glass production	250	160	90	40
Lead oxide and stabiliser production	350	340	10	< 10
Total	17,800	17,000	**800**	**400**
Source: Estimated on the basis of data supplied by the Lead REACH consortium *Note: All figures are 'order of magnitude' estimates. Totals may not sum due to rounding. Female workers of reproductive age are classed as being <46 years as per the data source*				

X10.4.3 UK HSE data

Data on workers subject to medical surveillance (blood lead levels) are also provided for the UK by the Health and Safety Executive. The data provided by UK HSE for 2016/17 are reproduced in the following table.

Table X10-9: Exposed workforce in the UK in 2016/17			
Sector	Men	Women	All
1: Smelting, refining, alloying and casting	923	52	975
2: Lead battery manufacture	674	21	695
3: Lead battery recycling	362	4	366
4: Badge and jewellery enamelling and other vitreous enamelling			
5: Glass making (including cutting and etching)	169	17	186
6: Glass recycling (including TV and monitors)	188		188
7: Manufacture of pigments and colours	8		8
8: Potteries, glazers and transfers	27	10	37
9: Manufacture of inorganic or organic lead compounds (including lead salts, fatty acids)	326	11	337
10: Shipbuilding, repairing and breaking	109		109
11: Demolition industry	399	2	401
12: Painting of buildings and vehicles	254	3	257
13: Paint removal	490	7	497
14: Work with metallic lead and lead containing alloys	571	41	612
15: Scrap industry (including pipes, flashing, cables)	464	8	472
16: Other processes	435	45	480
Total	***5,399***	***221***	***5,620***
Sources: HSE, Lead exposure, accessed at: http://www.hse.gov.uk/statistics/tables/exposure-to-lead.xlsx on 21 November 2018. *HSE (2017): Exposure to lead in Great Britain, 2017, accessed at: http://www.hse.gov.uk/statistics/causdis/lead/index.htm on 21 November 2018*			

X10.4.4 Breakdown by Member State

The UK HSE data reported above for the United Kingdom[410] have been extrapolated across the EU28 based on population; this exercise suggests a currently exposed workforce of around 50,000. Older sources may indicate higher values, for example, Carex-Esp from 2004 provides an estimate of over 67,000 exposed workers in Spain alone[411]. Since exposure is assumed to have decreased over time due to the introduction of various controls (see section on trends below), older sources are considered to overestimate current exposure. In terms of how appropriate different data are for this study, there may also be some issues with using the SUMER data referred to above, since as noted it may include potentially exposed workers i.e. respondents are identified as exposed when the agent is present at the place of work, irrespective of the duration or intensity of any exposure.

For the purposes of this study, the HSE data are therefore thought to provide a more realistic estimate of the number of workers actually exposed. This is supported by an Austrian response to the consultation, which suggested that there are around 1,400 workers exposed to lead. This figure is of a similar order of magnitude to the value of 900 estimated through extrapolation (bearing in mind that the HSE data do not include very low levels of exposure for short time periods).

Table X10-10: Historical potentially exposed workforce by Member State

Member State	Extrapolation from HSE (data from 2016/17)	
	Workers	%
Austria	800	2%
Belgium	900	2%
Bulgaria	600	1%
Croatia	300	1%
Cyprus	100	<1%
Czech Republic	900	2%
Denmark	500	1%
Estonia	100	<1%
Finland	500	1%
France	5,700	13%
Germany	7,100	16%
Greece	900	2%
Hungary	900	2%
Ireland	400	1%
Italy	5,200	12%
Latvia	200	<1%
Lithuania	300	1%
Luxembourg	<50	0.1%
Malta	<50	0.1%
Netherlands	1,400	3%
Poland	3,200	7%
Portugal	900	2%

[410] HSE (2017): Exposure to lead in Great Britain, 2017, accessed at: http://www.hse.gov.uk/statistics/causdis/lead/index.htm on 21 November 2018.

[411] Carex-Esp (2006): Sistema de Información sobre Exposición Ocupacional a Cancerígenos en España en el año 2004, accessed at: http://www.istas.ccoo.es/descargas/InformeCarex.pdf on 21 November 2018.

Table X10-10: Historical potentially exposed workforce by Member State		
Member State	Extrapolation from HSE (data from 2016/17)	
	Workers	%
Romania	1,700	4%
Slovakia	500	1%
Slovenia	200	<1%
Spain	4,000	9%
Sweden	900	2%
United Kingdom	5,600	13%
Total	44,000	100%
Note: totals may not sum exactly due to rounding. *Source:* *HSE (2017): Exposure to lead in Great Britain, 2017, accessed at:* *http://www.hse.gov.uk/statistics/causdis/lead/index.htm on 21 November 2018*		

X10.4.5 Trends

Data from the UK show a decreasing trend over the past decade in the number of workers under medical surveillance of around 2.9% per annum, although this is a long-term trend with some intervening years showing an increase in the number of workers subject to medical surveillance due to lead exposure (HSE, 2017). This trend follows on from previous decreases dating back to the 1990s (as per the following figure).

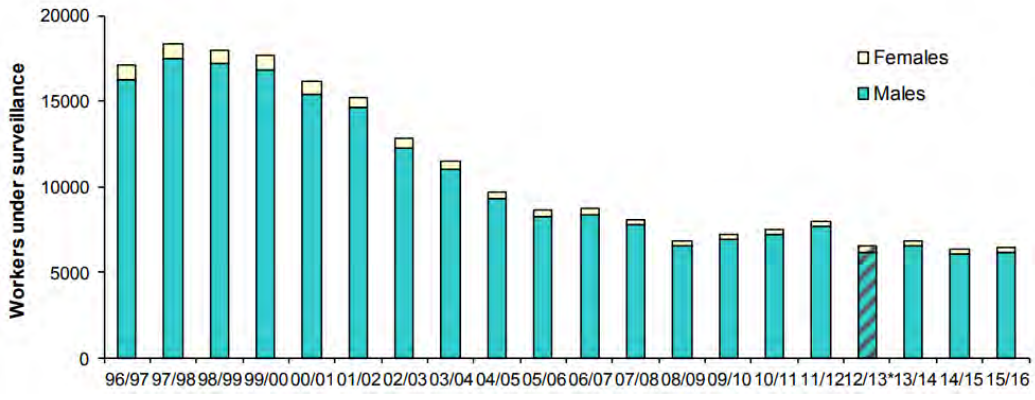


Figure X10-1: The total number of British lead workers under medical surveillance since 1996/97 by sex
Note: * Data for 2012/13 include a correction for previous undercutting
Source: http://www.hse.gov.uk/statistics/causdis/lead/index.htm accessed on 28 August 2018

It is expected that the number of workers exposed to lead compounds is likely to further decrease due to legislative developments set out earlier in this section.

X10.4.6 Exposed workers: conclusion

The total number of potentially exposed workers is summarised below.

Table X10-11: Potentially exposed workforce: conclusion			
Estimate	**Total no. of exposed workers**	**Men**	**Women**
Central estimate (based on ILA data)	18,000	17,000	800
High estimate (based on extrapolation of HSE data)	44,000	42,000	1,700 (all women)
Note: Totals also include women over reproductive age. Numbers are presented to two significant figures. Totals may not sum exactly due to rounding			

X10.5 Exposure levels

X10.5.1 Exposure levels

Average blood lead values by sector reported by the Lead REACH Consortium are shown below.

Table X10-12: Lead exposure levels by sector – average blood lead values – ILA 2013-2016 survey			
Sector	**Average blood lead values – women of childbearing age (µg/dL)**	**Average blood lead values – all women (µg/dL)**	**Average blood lead values – all workers (µg/dL)**
Lead battery producers	< 10	< 10	14
Primary lead producers	< 5	6	16
Secondary lead producers	< 5	6	17
Lead sheet producers	< 5	< 5	14
Ceramic ware production	11	12	13
Lead crystal glass production	7	8	11
Lead oxide and stabiliser producers	6	6	16
Source: Lead REACH consortium *Note: figures have been rounded and are based on four years of data (2013-16)*			

P90 blood lead levels are shown in the table below.

Table X10-13: Lead exposure levels by sector – P90 values across all samples reported in the ILA 2013-2016 survey	
Sector	**P90 blood lead values – all workers (µg/dL)**
Lead battery producers	29
Primary lead producers	27
Secondary lead producers	28
Lead sheet producers	30
Ceramic ware production	14
Lead crystal glass production	24
Lead oxide and stabiliser producers	28
Source: Lead REACH consortium *Note: figures have been rounded and are based on four years of data. For all sectors reported in this table, the P90 values for 2016 (the latest year for which data have been provided) are lower than the four-year combined values given here*	

Data for the UK (2016/17) are reproduced below.

Table X10-14: Lead exposure levels by sector – United Kingdom, male workers (2016/17)												
Sector	**Highest blood-lead measurement (µg/100ml) – male workers**											**Total male workers**
	<10	**10-19**	**20-24**	**25-29**	**30-34**	**35-39**	**40-49**	**50-59**	**60-69**	**70-79**	**>80**	
Smelting, refining, alloying and casting	407	296	70	68	28	28	22	3		1		**923**
Lead battery manufacture	170	273	106	72	41	11	1					**674**
Lead battery recycling	90	190	52	17	6	3	2		1	1		**362**
Badge and jewellery enamelling and other vitreous enamelling												
Glass making (including cutting and etching)	63	26	24	19	14	15	6	2				**169**
Glass recycling (including TV and monitors)	47	79	37	14	6	3	2					**188**
Manufacture of pigments and colours	8											**8**
Potteries, glazers and transfers	25		1				1					**27**
Manufacture of inorganic or organic lead compounds (including lead salts, fatty acids)	157	84	30	25	18	6	6					**326**

Table X10-14: Lead exposure levels by sector – United Kingdom, male workers (2016/17)												
Sector	Highest blood-lead measurement (µg/100ml) – male workers											Total male workers
	<10	10-19	20-24	25-29	30-34	35-39	40-49	50-59	60-69	70-79	>80	
Shipbuilding, repairing and breaking	95	12				2						**109**
Demolition industry	253	98	23	10	8	2	5					**399**
Painting of buildings and vehicles	166	48	11	9	10	3	7					**254**
Paint removal	311	81	24	22	14	12	13	7	6			**490**
Work with metallic lead and lead containing alloys	192	135	73	51	37	38	30	15				**571**
Scrap industry (including pipes, flashing, cables)	279	130	23	15	5	3	4	3	2			**464**
Other processes	328	70	11	10	9	4	3					**435**
Total	2,591	1,522	485	332	196	130	102	30	9	2	0	**5,399**
Source: *HSE, Lead exposure, accessed at: http://www.hse.gov.uk/statistics/tables/exposure-to-lead.xlsx on 21 November 2018*												

Table X10-15: Lead exposure levels by sector – United Kingdom, female workers (2016/17)												
Sector	Highest blood-lead measurement (µg/100ml) – female workers											Total female workers
	<10	10-19	20-24	25-29	30-34	35-39	40-49	50-59	60-69	70-79	>80	
Smelting, refining, alloying and casting	40	11	1									**52**
Lead battery manufacture	12	8	1									**21**
Lead battery recycling												**4**
Badge and jewellery enamelling and other vitreous enamelling												
Glass making (including cutting and etching)	14	3										**17**
Glass recycling (including TV and monitors)												
Manufacture of pigments and colours												
Potteries, glazers and transfers	9		1									**10**
Manufacture of inorganic or organic lead compounds (including lead salts, fatty acids)	10	1										**11**
Shipbuilding, repairing and breaking												
Demolition industry												**2**
Painting of buildings and vehicles												**3**

Table X10-15: Lead exposure levels by sector – United Kingdom, female workers (2016/17)												
Sector	Highest blood-lead measurement (µg/100ml) – female workers											Total female workers
	<10	10-19	20-24	25-29	30-34	35-39	40-49	50-59	60-69	70-79	>80	
Paint removal	5	1	1									**7**
Work with metallic lead and lead containing alloys	34	6	1									**41**
Scrap industry (including pipes, flashing, cables)	5	1	2									**8**
Other processes	35	9	1									**45**
Total	**173**	**40**	**8**									**221**
Source: *HSE, Lead exposure, accessed at: http://www.hse.gov.uk/statistics/tables/exposure-to-lead.xlsx on 21 November 2018*												

X10.5.2 Trends

Blood Lead Levels (BLL) have been dropping steadily over the past decades (OEHHA, 2013[412]).

The BLL trend for male workers under medical surveillance in the UK is provided in the following figure; please note that the figure only provided workers with blood levels above 50 µg/100ml).

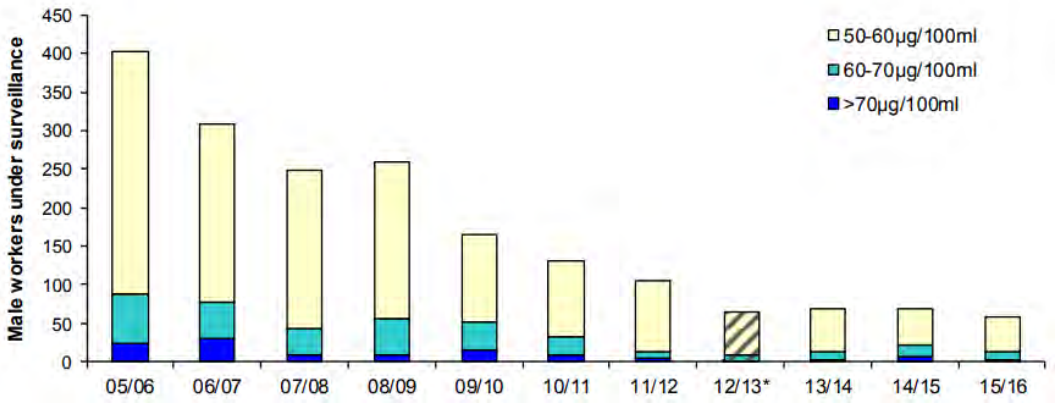


Figure X10-2: UK male workers with elevated blood levels (> 50 µg/100ml)
Note: * Data for 2012/13 include a correction for previous undercutting
Source: http://www.hse.gov.uk/statistics/causdis/lead/index.htm accessed on 28 August 2018

The BLL trend for female workers under medical surveillance in the UK is provided in the following figure; please note that the figure only shows workers with blood levels above 25 µg/100ml).

Longer term data covering the period since the early 1990s show a marked decline in the numbers of male and female workers with elevated blood lead levels (>40 µg/100ml and >25 µg/100ml respectively).

[412] Estimating Workplace Air and Worker Blood Lead Levels using an Updated Physiologically-based Pharmacokinetic (PBPK) Model, Off. Environ. Health Hazard Assessment, California Environmental Protection Agency, October 2013, accessed at: https://www.cdph.ca.gov/Programs/CCDPHP/DEODC/OHB/OLPPP/CDPH%20Document%20Library/OEHHALeadRept-Full.pdf on 21 November 2018.

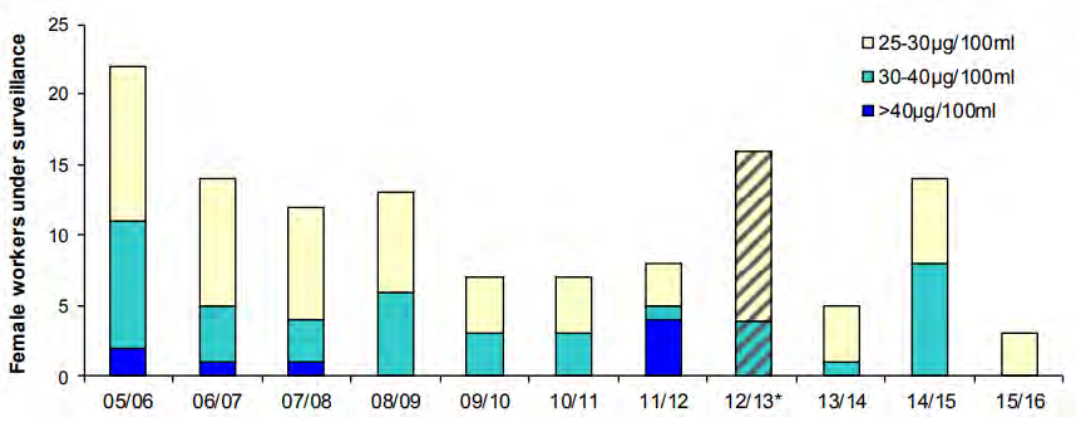


Figure X10-3: UK female workers with elevated blood levels (> 25 µg/100ml)
Note: * Data for 2012/13 include a correction for previous undercutting
Source: http://www.hse.gov.uk/statistics/causdis/lead/index.htm accessed on 28 August 2018

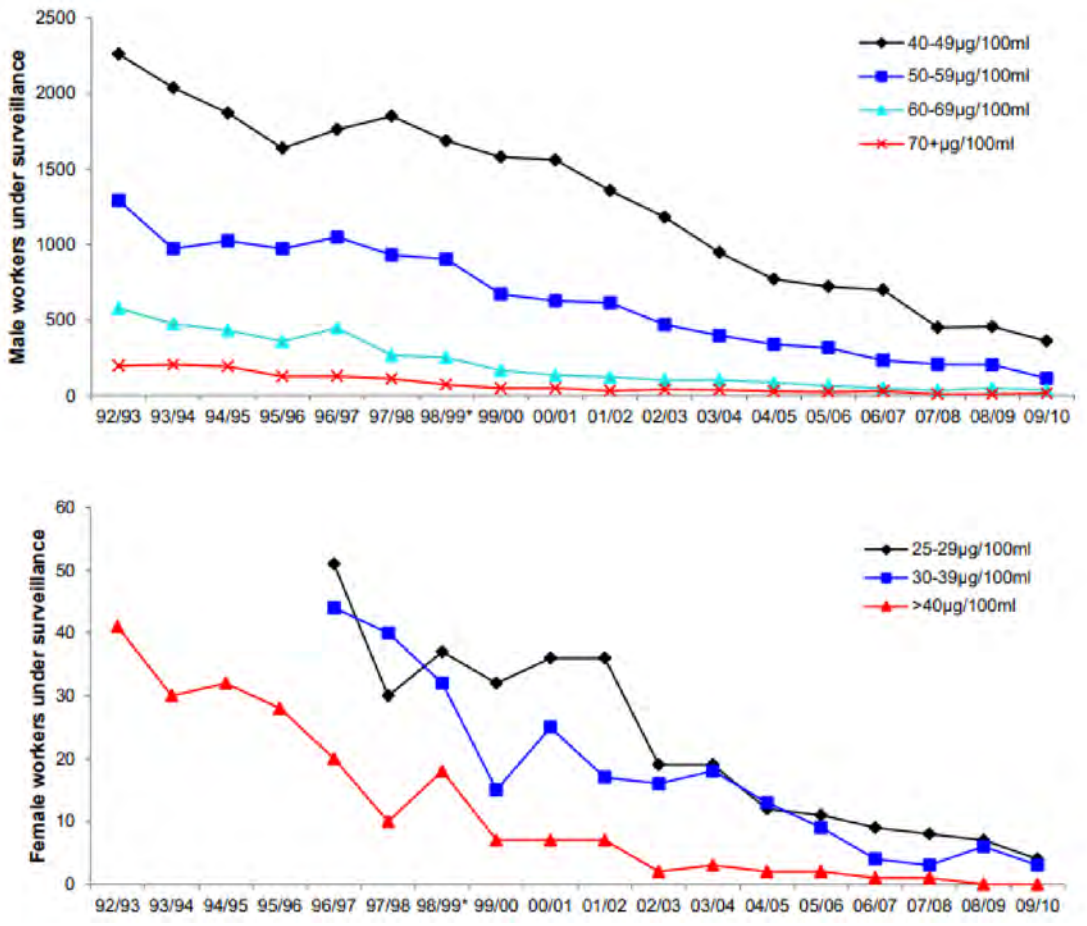


Figure X10-4: UK workers with elevated blood levels (> 40 µg/100ml for men and > 25 µg/100ml for women)
Source: http://www.hse.gov.uk/statistics/causdis/lead/blood-lead-trend-report.pdf accessed on 21 November 2018

BLLs are expected to be further reduced due to the industry's voluntary commitments.

Table X10-16: ILA Blood Level Reduction Programme

ILA's strategic objective is to encourage companies to continually reduce blood lead levels to as low as reasonably practicable, irrespective of perhaps more permissive regulatory occupational exposure limits in any given country. Under the current programme, lead battery manufacturers aim to achieve a 20µg/dL target by the end of 2025 (they have also established an interim milestone of 25µg/dL by the end of 2019); lead producers are committed to achieving the target of 20µg/dl as soon as reasonably practicable. Previously, the target was all employees below 30µg/dL blood at end of 2016. Note that the voluntary targets apply without prejudice to the 10µg/dL DNEL set under REACH for female employees of childbearing capacity.

A company's commitment to this continuous improvement in worker exposure is a condition of ILA membership. ILA members report to ILA each year the number of employees in a set blood lead ranges, and ILA uses that information to provide feedback to the ILA members, including benchmarking against their peers. ILA provides guidance to members on how to implement effective blood lead reduction programme on site, provides general support and a governance framework, and facilitates workshops/meetings for the members to share experiences and good practice.

Table X10-16: ILA Blood Level Reduction Programme
Action levels The ILA voluntary programme is developed with EUROBAT, given Pb batteries are the major (~90+%) Pb use sector. In REACH dossiers and SDS templates, the Lead REACH Consortium provides guidance in the exposure assessment, in particular: "The blood lead levels of workers will be monitored on a regular basis, often in reference to an "action level" that is typically 5 µg/dL below the exposure limit deemed to be safe. If the action level is exceeded, appropriate measures are to be taken, (e.g. ban overtime, provide counselling on proper work practice and hygiene, instigate an individual blood lead management plan, increase blood lead sampling frequency) in an effort to prevent further increases in blood lead. If the safe threshold (40 µg/dL for men; 10 µg/dL for women of reproductive capacity) is exceeded, continue ban on overtime, ensure strict hygiene procedures are followed, undertake detailed inspections to ensure correct use of personal protective equipment, undertake detailed inspections to ensure recommended workplace procedures are followed, move employee to workplace where exposure is expected to be lower or remove from lead environment altogether, further increase blood lead sampling frequency, and continue frequent sampling until results are below the first action level."
Sources: *Information provided by the ILA to the study team* *Safety data sheet, Litharge, accessed at: http://www.klen.com.au/CRM/Certificates_of_Analysis/Litharge-1.pdf on 21 November 2018.* *ILA News, accessed at: https://www.ila-lead.org/news/ila-news/2017-06-15/lead-and-lead-battery-industries-announce-ambitious-new-targets-to-protect-workers on 21 November 2018.* *EUROBAT (2013): Industry exposure trends, voluntary blood lead reduction programmes, presentation given by Michel Baumgartner, EU Affairs Manager in Prague, June 2013, accessed at: https://www.ila-lead.org/UserFiles/File/conferences/pb2013/conference-files/Workshop%20PPTpdfs/W.1.4.b.%20Michel%20Baumgartner.pdf on 21 November 2018.* *ILA guidance, accessed at: https://www.ila-lead.org/UserFiles/File/guidancenotes/ILA_GN_General_V04.pdf on 21 November 2018*

X10.6 Market analysis

X10.6.1 Overview

The Lead REACH Consortium includes around 90 companies that manufacture or import lead or its compounds into the EU[413]. These include companies in sectors such as metals and batteries. The Association of European Manufacturers of Sporting Ammunition (AFEMS) is an associate member.

According to EUROBAT, there are 31 lead-based battery plants that are situated in 14 EU Member States which employ approximately 20,000 workers. The sector's annual turnover is €5 billion and its R&D expenditure over the past five years has been in excess of €845 million. In addition, lead-based battery recyclers have facilities in 15 EU Member States[414].

The socio-economic characteristics of the sectors in which lead exposure may occur are summarised below.

- C20: Manufacture of chemicals and chemical products

[413] Lead Reach Consortium, Members, accessed at: https://ila-reach.org/the-consortium/members/ on 21 November 2018.

[414] EUROBAT, EUROBAT Position - Annex XV SVHC report published in the context of SVHC identification in accordance with REACH Article 57 – Lead, accessed at: http://www.eurobat.org/images/news/position-papers/23042018_EUROBAT_Position_Paper_on_Annex_XV_Report_on_Lead_Metal.pdf on 21 November 2018.

- C20.3: Manufacture of paints, varnishes and similar coatings, printing inks and mastics
- C20.51: Manufacture of explosives
- C22.1: Manufacture of rubber products
- C22.2: Manufacture of plastic products
- C25: Manufacture of fabricated metal products, except machinery and equipment
- C26: Manufacture of computer, electronic and optical products
- C27: Manufacture of electrical equipment
- C29: Manufacture of motor vehicles, trailers and semi-trailers
- G: Wholesale and Retail Trade; Repair of Motor Vehicles and Motorcycles

X10.6.2 Proportion of SMEs in each sector

The following table provides the proportion of SMEs by size of enterprise and sector.

Table X10-17: Proportion of SMEs by size of enterprise and sector				
Sector	Micro	Small	Medium	Large
	% of total	% of total	% of total	% of total
C20	66%	21%	10%	3%
C20.3	58%	28%	11%	3%
C20.5	64%	24%	11%	2%
C22.1	66%	23%	8%	3%
C22.2	65%	24%	9%	1%
C25	82%	15%	3%	0%
C26	75%	17%	6%	2%
C27	74%	17%	7%	2%
C29	62%	20%	12%	7%
G	93%	6%	1%	0%
Source: Eurostat's Structural Business Statistics database				

X10.7 Burden of ill health

X10.7.1 Summary of the assessment framework

Summary of the scenarios

The numbers of cases of reproductive ill health have been estimated for the following three scenarios:

- **Scenario L1:** A scenario modelled on the average exposure values reported in the 2013-16 Lead REACH Consortium survey. This scenario reflects the assumption that where a worker exceeds the ILA target of BLL 30 µg/ dL or 10µg/dL DNEL set under REACH for female employees of childbearing capacity, they would normally be removed from exposure until their BLL declines, thus assuming that samples obtained from each worker can have different values that, over a period of time, will converge on the averages reported in the ILA dataset. Average values are available from the ILA database for all workers, women, and women of reproductive age (<46 years)[415]. The disadvantage of this scenario is that average values for an entire sector reflect a range of BLL values which include some workers with significantly

[415] Note that the category is defined as being <46 years for consistency with the dataset provided.

higher BLLs. This method is therefore likely to underestimate the health effects of lead exposure.

- **Scenario L2:** This scenario uses the available data from the Lead REACH Consortium (average BLL values for women of reproductive age and the average, P75 and P90 BLL values for all workers) to estimate the distribution of male and female (<46y) workers over the different BLL deciles between the min. and max. values reported by the ILA. A separate distribution is estimated for each sector. The number of cases of reproductive ill health is estimated for each effect by sector and exposure decile. This scenario reflects the assumption that, since lead is stored in the bone and BLL takes a long time to decline (see the following table for the number of days to decline to BLL 15 µg/dL), workers generally maintain a relatively constant BLL over relatively long periods of time. However, it should be noted that the BLL measurement data are provided for a period between 2013 and 2016 and extended removal from exposure would have been possible during this period. This method may overestimate the effects of lead exposure.

Table X10-18: BLL time to decline to 15 µg/dL after removal from workplace (OEHHA 2013[416])						
Exposure duration	Percentile	BLL at beginning of Medical Removal Protection (µg/dL)				
		20	30	40	50	60
		Days to decline to 15 µg/dL				
1 year	50th	21	128	280	435	615
	90th	38	234	511	795	1,123
	95th	45	277	605	940	1,329
10 years	50th	31	200	400	630	920
	90th	57	365	731	1,151	1,681
	95th	67	432	865	1362	1,989
25 years	50th	32	207	416	670	1,005
	90th	58	378	760	1,224	1,836
	95th	69	447	899	1,448	2,172
40 years	50th	32	210	425	685	1,045
	90th	58	384	776	1,251	1,909
	95th	69	454	919	1,481	2,259

In order for these P90 values to decline to 15 µg/dL, it would require removal from lead exposure on the order of magnitude of 7 months plus at the 50th percentile and up to 15 months at the 95th percentile (BLL ~ 30 µg/dL). As an illustration, the following figure indicates the number of UK lead workers under medical surveillance who have been suspended from working with lead since 2005/06.

[416] Estimating Workplace Air and Worker Blood Lead Levels using an Updated Physiologically-based Pharmacokinetic (PBPK) Model, Off. Environ. Health Hazard Assessment, California Environmental Protection Agency, October 2013, accessed at: https://www.cdph.ca.gov/Programs/CCDPHP/DEODC/OHB/OLPPP/CDPH%20Document%20Library/OEHHALeadRept-Full.pdf on 21 November 2018.

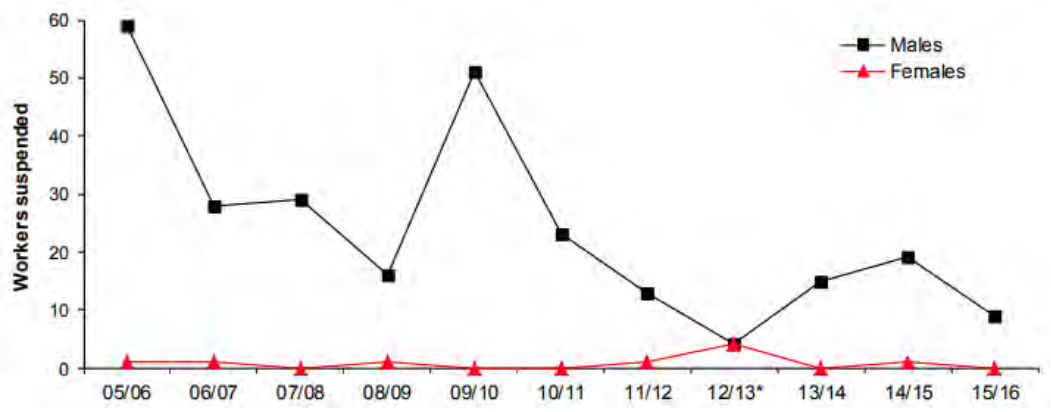


Figure X10-5: Number of male and female lead workers under medical surveillance suspended from working with lead since 2005/06
Note: * Data for 2012/13 include a correction for previous undercutting
Source: http://www.hse.gov.uk/statistics/causdis/lead/index.htm accessed on 4 February 2019

- **Scenario L3:** This scenario uses 2016/17 blood level data from medical surveillance in the UK reported by the UK Health and Safety Executive (HSE)[417] (see earlier section on exposure levels for UK data by sector). This dataset appears to encompass more industry sectors than the ILA dataset but, since these data are only available for the UK, they may not be representative of other EU Member States. Under Scenario L3, these data have been extrapolated over the entire EU, based on the UK's share in the total EU population.

Overview of monetisable effects and toxicological/epidemiological endpoints

The effects taken forwards for monetisation in this study are summarised below. Note that health effects have only been included where they can be monetised. Whilst it may be possible to monetise other, additional effects, this study has not done so to avoid potential double counting between effects where the same end point (i.e. the same monetisable effect) may be used in the calculations.

Table X10-19: Lead – summary of health effects

Monetisable effect	Health effect	Threshold BLL (µg/dL)	Slope (% /µg/dL))	Maximum value of slope applicability BLL (µg/dL)	Outcome – Fer/Dev		Cause - Exposed workers	
					Fer	Dev	F	M
Spontaneous abortion or still birth	Increased Odds ratio for spontaneous abortion	5	13	Could not be derived	F0f		F	
	Increased incidence of stillbirth	>30	2.83	786	F0f		F	
Low birth weight	Increased frequency of preterm births	5 (0.98)	34.12	9.77		F1fm	F	
	Reduced foetus weight at birth	>30	-0.38	390		F1fm	F	

[417] HSE, Index of data tables, lead exposure, accessed at: http://www.hse.gov.uk/statistics/tables/#lead on 22 November 2018.

Table X10-19: Lead – summary of health effects								
Monetisable effect	Health effect	Threshold BLL (µg/dL)	Slope (% /µg/dL))	Maximum value of slope applicability BLL (µg/dL)	Outcome – Fer/Dev		Cause - Exposed workers	
					Fer	Dev	F	M
Impaired fertility - male	Impaired male fertility (fraction of workers affected)	25	0.002	60	F0m			M
Impaired fertility - female	Reduced number of foetuses/dam	>30	-0.77	390	F0f		F	
Pre-eclampsia	Pre-eclampsia (additional incidence)	5	0.016	15	F0f		F	
IQ loss	IQ loss in children (IQ points lost per child)	5 (1.7)	0.14	40		F1fm	F	
Note: Slope for IQ loss in children represents loss of IQ points per 1µg/dl								

Establishing a quantitative relationship between percentage change in the tox/epi effect and a monetisable endpoint

The methods used to translate an estimated percentage change for an effect given in the literature (e.g. reduced foetus weight at birth) into the number of cases for a corresponding monetisable effect (e.g. low birth weight) are summarised in the table below. Detailed intermediate calculations are not provided due to data confidentiality.

Table X10-20: Lead – approach to calculation of the numbers of cases		
Monetisable effect	DRR effect	Approach to estimating the number of cases
Spontaneous abortion & stillbirth	Increased odds ratio for spontaneous abortion	**Step 1:** DRR provides: % increase over estimated OR=1.8 at BLL 5 µg/dL (estimated from Borja-Aburto, 1999) **Step 2:** 2.83% of female workers give birth each year but only 30% of conceptions result in birth, with 70% conceptions being lost due to implantation failure (30%), early pregnancy loss (30%) and clinical miscarriage (10%)[418]. The incidence rate of spontaneous abortion/stillbirth used in this study is 8%-20%. Taking into account the incidence of stillbirth[419], suggests that around 14% of conceptions are lost due to spontaneous abortion (i.e. without them the number of births would be 50% higher). This suggests that 1% of the female workforce suffers from a 'clinically recognisable' spontaneous abortion each year. **Step 3:** The OR indicates the increase for female lead workers that is above the 14% incidence rate among female workers not exposed to lead **Step 4**: This increase is applied to the number of female workers expected to give birth each year and estimated to be above the threshold. Note that where workers have different blood lead levels (e.g.

[418] See the pregnancy loss iceberg, accessed at: https://www.researchgate.net/figure/The-Pregnancy-Loss-Iceberg-an-overview-of-the-outcome-of-spontaneous-human-pregnancy-A_fig1_11183246 on 22 November 2018.

[419] Tommy's, Stillbirth Statistics, accessed at: https://www.tommys.org/our-organisation/charity-research/pregnancy-statistics/stillbirth on 22 November 2018.

Table X10-20: Lead – approach to calculation of the numbers of cases		
Monetisable effect	**DRR effect**	**Approach to estimating the number of cases**
		in scenarios 2 and 3), several calculations are performed with the results then summed
	Increased incidence of stillbirth	**Step 1:** As a worst-case scenario, it is assumed that stillbirth occurs in the case of 1% of deliveries[420] (of 2.83% of female workers of reproductive age that give birth each year, i.e. 0.0283% of female workers) **Step 2:** The DRR result signifies a % increase over this rate **Step 3:** The increase is applied to the number of female workers expected to give birth each year and estimated to be above the threshold. As above, where workers have different blood lead levels (e.g. in scenarios 2 and 3), several calculations are performed with the results summed
Low birth weight	Increased frequency of preterm births	**Step 1:** The incidence of preterm birth can be equated with the incidence of low birth weight since pre-term births ae a subset of low birth weight. **Step 2:** At OR=1, the incidence is 6.5% of births **Step 3:** The increase is applied to those female workers whose blood lead level is above the threshold (assumed to be 5 µg/dL), with separate calculations performed for workers with different concentrations under scenarios 2 and 3
	Reduced foetus weight at birth	**Step 1:** DRR result shows reduction in birth weight. This is 3.85% for female workers that give birth. **Step 2:** Distribution of babies by birth weight suggests that a small proportion of babies (estimated 0.25%) is at risk of experiencing negative effects **Step 3:** This increased risk is applied to workers with blood lead levels above the threshold (30 µg/dL)
Impaired fertility - male	Reduction in fertility	Already expresses as fraction of workers affected with 0.002% reduction in fertility per µg/dl increase in blood lead level over the threshold. This percentage is applied to all workers over the threshold, taking into account the µg/dl by which each worker is above the threshold
Impaired fertility - female	Reduced number of foetuses / dam	Assumption - Reduced number of foetuses / dam is interpreted as % change in pregnancy rate. Similarity of response[421] for pregnancy rate & reduced number of foetuses per dam suggests this is an acceptable assumption. Percentage change in pregnancy rate is applied to those workers above the threshold (assumed to be 30 µg/dL)
Pre-eclampsia	Pre-eclampsia	**Step 1:** The DRR provides the risk of pre-eclampsia for expectant mothers. **Step 2:** The risk rate is applied to the 2.83% of female workers of reproductive age who are assumed to give birth in any given year
IQ loss (children)	IQ loss	**Step 1:** The DRR relates to change in child IQ according to blood lead level. **Step 2:** Blood lead level of child is assumed to be 90% of the mother's level, with 2.83% of female workers of reproductive age assumed to give birth each year and each child assumed to be affected

[420] Tommy's, Stillbirth Statistics, accessed at: https://www.tommys.org/our-organisation/charity-research/pregnancy-statistics/stillbirth on 22 November 2018.

[421] EHCA, lead, accessed at: https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/16063/7/9/2/?documentUUID=ffe391a7-ca3a-4bf6-a005-a1936532e275 on 22 November 2018.

Table X10-20: Lead – approach to calculation of the numbers of cases		
Monetisable effect	**DRR effect**	**Approach to estimating the number of cases**
		Step 3: Where the mother's blood lead level multiplied by 0.9 is above the threshold, the child is assumed to be affected with the loss in IQ dependent on the extent to which the threshold is exceeded

X10.7.2 Cases of ill health

The results of the three scenarios are summarised below.

Table X10-21: Lead – number of cases per annum estimated under each of the scenarios				
Monetisable effect	**DRR effect**	**Scenario L1**	**Scenario L2**	**Scenario L3**
Spontaneous abortion & stillbirth	Increased odds ratio for spontaneous abortion	2.5	14	7.3
	Increased incidence of stillbirth	0	0.002	0
	Total	*2.5*	*14*	*7.3*
Low birth weight	Increased frequency of preterm births	0.8	0.6	0.6
	Reduced foetus weight at birth	0	0.001	0
	Total	*0.8*	*0.6*	*0.6*
Impaired fertility - male	Reduction in fertility	0	95	115
Impaired fertility - female	Reduced number of foetuses / dam	0	1.6	0
Pre-eclampsia	Pre-eclampsia	0.6	0.7	0.9
IQ loss (in children)	Children affected (total IQ points lost)	12 (3.3)	7.7 (7.5)	5.7 (8.0)
Total number of cases		***16***	***120***	***129***

X10.8 Future developments

The calculations are based on data for 2013-16 (Lead REACH Consortium) and 2016/17 (UK HSE data). Over the long-term, there have been decreases in both the exposed workforce and BLL levels. This is a long-term trend which has been interrupted by increases in the exposed workforce several times. Future decreases are likely to further reduce the risk for those effects which have a threshold above the BLL caused by background exposure (e.g. impaired male fertility).

Annex 11 Bisphenol A (BPA)

X11.1 Introduction

X11.1.1 Relevant substance(s)[422]

4,4'-Isopropylidenediphenol (Bisphenol A, BPA) (EC No: 201-245-8; CAS No: 80-05-7) has a chemical formula of: $C_{15}H_{16}O_2$. It is also known by a large number of other names, including:

- 2,2-Bis(4-hydroxyphenyl) propane;
- 4,4'-(Propane-2,2-diyl)diphenol; and
- p,p'-Isopropylidenebisphenol.

The chemical structure of BPA is reproduced below.

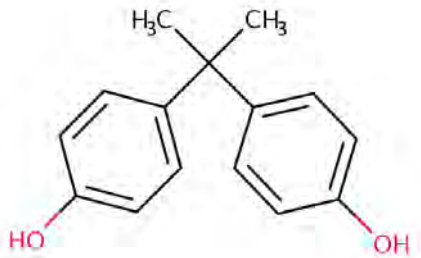


Figure X11-1: BPA – chemical structure
https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID7020182

X11.1.2 Hazard classification(s)

BPA has the following classifications:

- Repr. 1B (Hazard Statement Code H360F: May damage fertility);
- Specific Target Organ Toxicity (Single Exposure) (STOT-SE 3) (Hazard Statement Code H335: May cause respiratory irritation);
- Eye Dam. 1 (Hazard Statement Code H318: Causes serious eye damage); and
- Skin Sens. 1 (Hazard Statement Code H317: May cause an allergic skin reaction).

BPA was recently reclassified from R2 to R1B; the new classification has been in place since March 2018.

X11.1.3 Existing OELs and BLVs

The OELs and BGVs in EU Member States are summarised below. In addition, a number of countries have designated Bisphenol A as a dermal irritant (e.g. the Czech Republic, Hungary, Ireland, Lithuania).

[422] http://www.commonchemistry.org/ChemicalDetail.aspx?ref=80-05-7

Table X11-1: OELs and BGVs for Bisphenol A in the EU		
Country	**OELs 8-hr TWA Binding (unless stated otherwise)**	**BGVs**
Austria	5 mg/m³ inhalable aerosol	
Belgium	10 mg/m³	
Bulgaria	10 mg/m³ (respirable dust)[423]	
Croatia	10 mg/m³ (total dust)[424]	
Cyprus		
Czech Republic	2 mg/m³ (dust, aerosol)[425]	
Denmark	3 mg/m³ or 2 mg/m3[426]	
Estonia	10 mg/m³ (inhalable)[427]	
Finland	5 mg/m³	
France	10 mg/m³ (restrictive statutory limit)	
Germany	5 mg/m³ inhalable aerosol (Y[428])	BGV: total urinary bisphenol A, after hydrolysis, at 80 mg/L (at the end of the shift)[429] (Germany)
Greece	10 mg/m³ [430]	
Hungary	10 mg/m³ [431]	
Ireland	10 mg/m³ (indicative) [432]	
Italy	10 mg/m³	
Latvia	5 mg/m³	
Lithuania	10 mg/m³ (respirable dust)	
Luxembourg	10 mg/m³ [433]	
Malta	2 mg/m³ (inhalable)[434]	
Netherlands	10 mg/m³ (Gestis & RIVM) 2 mg/m³ (inhalable), 5 mg/m³ (respirable)	
Poland	5 mg/m³	
Portugal	10 mg/m³ [435]	
Romania	10 mg/m³	

[423] Regulation No 13 on protection of workers from exposure to chemical agents at work (D.V.8/2004, as amended through, January 6, 2012, D.V. 2/2012)

[424] Dangerous Substance Exposure Limit Values in the Workplace (OELs), Annexes 1 and 2, as amended through June 20, 2013(NN 75/2013)

[425] Government Decree 361/2007 Sb., amended through 9/2013 Sb., January 14, 2013

[426] Grænseværdier for stoffer og materialer. Arbejdstilsynet, An 2 & 3, amended byOrder No. 655, 2 June 2018

[427] Annex of Regulation No. 293 of 18 September 2001), as amended November 2011

[428] Y designation: Compliance with OEL and BLV values means no risk of reproductive damage. See https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Regelwerk/TRGS/pdf/TRGS-900.pdf? blob=publicationFile

[429] See the MAK and BAT list 2017, p. 235, available at https://onlinelibrary.wiley.com/doi/pdf/10.1002/9783527812127

[430] Decree 307/1986, last amended by Decree No. 12/2012, 9 February 2012

[431] 25/2000 Joint decree on chemical safety of workplaces 2000, as amended by 2011 MK, no. 2011/157, page 38588, 22 December 2011

[432] 2016 Code of Practice for Chemical Agents Regulations 2001, (S.I. No. 619 of 2001)

[433] Binding Occupational Exposure Limit Values (Annex I), Memorial A, no. 168, p. 2886, 8 August 2011

[434] Protection of Health and Safety of Workers from Risks related to Chemical Agents at Work (L.N 227/2003 Schedules I and V as amended through L.N. 57/2018, February 23, 2018)

[435] Decree-Law No. 24/2012, Occupational Exposure Limit Values, Annex III (Diário da República - I.a série - No. 26, 6 February 2012)

Table X11-1: OELs and BGVs for Bisphenol A in the EU		
Country	**OELs 8-hr TWA Binding (unless stated otherwise)**	**BGVs**
Slovakia	2 mg/m³ [436]	
Slovenia	5 mg/m³ (inhalable fraction) [437]	
Spain	2 mg/m³ [438]	
Sweden	2 mg/m³	
United Kingdom	10 mg/m³ (recently lowered to 2 mg/m³)[439]	
EU	2 mg/m³ (indicative, inhalable dust)[440] Previous indicative OEL: 10 mg/m³	SCOEL recommendation (BGV): 7 µg/l (urinary total bisphenol-A)[441]
Sources (for sources of data for specific Member States see the footnotes): DGUV Gestis, http://limitvalue.ifa.dguv.de/ Chemical Watch (2017): https://chemicalwatch.com/crmhub/57855/bisphenol-a-dutch-experts-call-for-new-oel MST (2014): Background for national legislation on bisphenol A (BPA) in EU and EFTA countries, available at https://www2.mst.dk/Udgiv/publications/2014/03/978-87-93178-18-2.pdf RIVM (2014): Overview of Occupational Exposure Limits within Europe, https://www.rivm.nl/bibliotheek/rapporten/2014-0151.pdf Notes: Shaded OELs – unclear whether indicative or binding.		

The DNELs (Derived No Effect Levels)[442] for occupational exposure to BPA are summarised below:

- DNEL for workers via inhalation route
  - The occupational long term DNEL for worker inhalation hazard is set at **2 mg/m³** for repeated dose toxicity.
  - The occupational short term DNEL for worker inhalation hazard is set at **2 mg/m³** for repeated dose toxicity.
  - The occupational long term DNEL for worker local effects hazard is set at **2 mg/m³** for irritation (respiratory tract).
  - The occupational short term DNEL for worker local effects hazard is set at **2 mg/m³** for irritation (respiratory tract).
- DNEL for workers via dermal route
  - The occupational long term DNEL for worker dermal hazard is set at **0.031 mg/kg bw/day** for repeated dose toxicity.

[436] http://www.epi.sk/zz/2006-355#prilohy
[437] ULRS 100/2001 as amended through June 4, 2015
[438] Valores Límites Ambientales (VLAs), Límites de Exposición Profesional Para Agentes Químicos en 2018
[439] Calculations carried out in this report still rely on 10 mg/m³ in the UK, Source: http://www.hse.gov.uk/pubns/priced/eh40.pdf
[440] Date of transposition 21st August 2018, Commission Directive (EU) 2017/164, available at https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32017L0164#ntr8-L_2017027EN.01011901-E0008
[441] This value is recommended for the identification of occupationally exposed from non-exposed. SCOEL (2014): "In the general population, urinary BPA levels are usually below 7 µg/l (95th percentile based on German and Canadian studies)." See http://ec.europa.eu/social/BlobServlet?docId=3873&langId=en
[442] https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/15752/7/1

- The occupational short term DNEL for worker dermal hazard is set at **0.031 mg/kg bw/day** for repeated dose toxicity.

The Limit of Quantificationb (LoQ) for sampling over 4 hours is 1.42 µg/m^3 in OSHA (2013)[443]. It is thus expected that the DNEL is measurable.

X11.1.4 Legislation other than CAD

This section screens out the uses that are mentioned in literature but that are no longer relevant due to regulatory or voluntary phase outs.

Relevant measures include[444]:

- Restricted in thermal paper with effect from 2020[445];
- Classified in the EU as a substance that has toxic effects on our ability to reproduce. All manufacturers, importers, or suppliers of BPA must classify and label mixtures containing BPA as toxic for reproduction category 1B by 1 March 2018[446];
- Bisphenol A was listed in the Candidate List of Substances of Very High Concern (SVHCs) due to its toxic for reproduction properties in January 2017. In January 2018, the BPA entry was updated to reflect an additional reason for inclusion in the Candidate List which is its endocrine disrupting properties.[447] However, with regard to a potential future authorisation requirement, it should be noted that BPA is predominantly used as an intermediate in the production of polycarbonate and epoxy resins. However, there are also non-intermediate uses of BPA, e.g. the use of BPA as an additive. The Risk Management Options Analysis RMOA) of BPA elaborated by the German authorities reportedly concludes that "the vast majority of uses is outside the scope of authorisation." [448]
- BPA has been banned from infant feeding bottles across the EU since 2011 and a similar ban is being discussed for plastic bottles and packaging containing food for babies and children under three years old. There are migration limits for BPA leaching from food contact materials and toys.[449];
- Austria and Germany ban BPA in pacifiers and teething rings (in Austria, this includes a ban on the use of BPA in the manufacture of such items)[450];
- Since 2016, Sweden has in place a restriction on the use of BPA in 2-component epoxy resin for relining of water pipes[451]; and

[443] https://www.osha.gov/dts/sltc/methods/validated/1018/1018.pdf
[444] Unless stated otherwise, taken from https://echa.europa.eu/hot-topics/bisphenol-a
[445] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2016.337.01.0003.01.ENG&toc=OJ:L:2016:337:TOC
[446] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R1179
[447] https://echa.europa.eu/candidate-list-table; https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2016.195.01.0011.01.ENG&toc=OJ:L:2016:195:TOC; https://echa.europa.eu/-/seven-new-substances-added-to-the-candidate-list-entry-for-bisphenol-a-updated-to-reflect-its-endocrine-disrupting-properties-for-the-environment
[448] https://chemicalwatch.com/63607/european-plastics-trade-group-opposes-latest-bpa-decision
[449] https://echa.europa.eu/hot-topics/bisphenol-a
[450] MST (2014): Background for national legislation on bisphenol A (BPA) in EU and EFTA countries, available at https://www2.mst.dk/Udgiv/publications/2014/03/978-87-93178-18-2.pdf
[451] http://www.bisphenol-a-europe.org/regulatory-framework/national-legislation/

- Belgium, Sweden and Denmark ban BPA from food contact materials for infants and children under three years and France bans BPA in all food packaging, containers and utensils.[452]

Recently, there have also been changes at the EU level to migration limits for BPA in food contact materials and toys.[453] It is possible that this may provide an incentive for companies to reduce BPA use.

X11.2 Summary of health endpoints, thresholds & DRRs

X11.2.1 Relevant health endpoints

Relevant reproductive health endpoints

The reproductive effects identified through literature review are summarised below. The table below only lists adverse effects which have been deemed as potentially relevant to humans (i.e. they have a potential for human effects correlation), a no-effect threshold and a Dose-Response Relationship (DRR) could be derived and the source of the data is not a study that is clearly irrelevant to occupational exposure.

Table X11-2: BPA – summary of health effects

Health effect identified in literature	Fertility/ development?		Monetisable effect correlate
	Fer	Dev	
Decreased seminal vesicle weight in F1 males		Dev	Impaired fertility – male offspring*
Decrease in # of live pups/litter	Fer		Spontaneous abortion/still-birth
Decrease in mean # pups	Fer		Impaired fertility – male Impaired fertility - female
Decrease in # of live pups	Fer		Spontaneous abortion/still-birth
Decrease in mean # litters/pair	Fer		Impaired fertility – male Impaired fertility – female
Increase in cumulative days to litter		Dev	Reduced foetal growth/low birth rate
Decreased epididymal sperm concentration (**F0**)	Fer		Impaired fertility – male
Epithelial hyperplasia (Vagina) (Continuous dose-terminal)**	Fer		Impaired fertility – female
Dilatation of lumen in uterus (Continuous dose-terminal)**	Fer		Impaired fertility – female
Increased paired ovarian primordial follicle count (**F0**)	Fer		No monetisable effect correlate[454]
Reduced epididymal sperm concentration (**F1**)***		Dev	Impaired fertility – male offspring*
Reduced daily sperm production/testis (**F3**)***		Dev	Impaired fertility – male offspring*
Increased gestational length (F0 and **F1**)	Fer	Dev	Impaired fertility – female Impaired fertility – male offspring*

[452] https://www2.mst.dk/Udgiv/publications/2014/03/978-87-93178-18-2.pdf and https://echa.europa.eu/hot-topics/bisphenol-a

[453] See https://echa.europa.eu/hot-topics/bisphenol-a

[454] Although it could be argued that this effect may reflect a lower number of eggs are produced per cycle and it could thus be assumed to have the effect of reducing the likelihood of a woman becoming pregnant, this is not seen as sufficiently strong to establish a correlation with a monetisable effect.

Table X11-2: BPA – summary of health effects			
Health effect identified in literature	Fertility/ development?		Monetisable effect correlate
	Fer	Dev	
Decreased mean pup body weight/litter-PND-21-male (**F1**)		Dev	No monetisable effect correlate
Decreased mean pup body weight/litter-PND-21-female (**F1**)		Dev	No monetisable effect correlate
Notes: Fertility effects on F1 are treated as 'developmental' in this table. All effects observed in multiple generations assigned to the earliest generation, e.g. F2 and F3 assigned to F1 for monetisation purposes, using the probabilities for F3 as the worst-case scenario. Effects observed in F1 have been assigned to both F0 and F1, using the F1 probabilities for both F0 and F1 as the worst-case scenario. *Only male offspring fertility monetary value has been identified and all cases of impaired fertility in F1 are therefore valued as 'impaired fertility – male offspring'. **These effects are considered together. ***These effects reflect the same underlying change and are therefore considered together.			

Other health endpoints

In addition to the effects that relate to the hazard classifications for BPA listed above, a number of other potentially relevant non-reprotoxic effects on the parents have been identified:

- Increased haemoglobin-Female
- Increased haemoglobin-Male
- Decreased platelets-Male
- Increase in the incidence of female mammary gland adenocarcinoma
- The combination of adenoma and adenocarcinoma
- Hyperplasia, transitional epithelium (Kidney)-Male
- Cystic degeneration (Liver)-Female
- Maternal body weight exhibited a statistically significant downward trend
- Increased liver weight (F0)
- Increased left kidney weight (F0)

X11.2.2 Summary of thresholds and DRRs

The no effect thresholds (inhalation 8-hr TWA mg/m3) and effect slopes, together with the maximum air exposure concentrations (8-hr TWA mg/m3) for which the effect slopes are valid, are summarised below. For a more detailed overview of how these values were derived, refer to Annex 1.

Table X11-3: BPA – effects, thresholds and DRRs				
Health effect	Threshold (mg/m^3)	Slope (% effect change/ mg/m^3)	Maximum range of slope applicability (mg/m^3)	Monetisable effect correlate
Decreased seminal vesicle weight in F1 males	43.8	-2.54	437.8	Impaired fertility – male offspring*
Decrease in # of live pups/litter	87.5	-2.41	875.5	Spontaneous abortion/still-birth

Table X11-3: BPA – effects, thresholds and DRRs				
Health effect	**Threshold (mg/m^3)**	**Slope (% effect change/ mg/m^3)**	**Maximum range of slope applicability (mg/m^3)**	**Monetisable effect correlate**
Decrease in mean # pups	175	-1.52	1750	Impaired fertility – male Impaired fertility - female
Decrease in # of live pups	175	-3.17	1750	Spontaneous abortion/still-birth
Decrease in mean # litters/pair	87.5	-0.51	875.5	Impaired fertility – male Impaired fertility – female
Increase in cumulative days to litter	175	0.57	1750	Reduced foetal growth/ low birth rate
Decreased epididymal sperm concentration (**F0**)	50.0	-0.03	600	Impaired fertility – male
Epithelial hyperplasia (Vagina) (Continuous dose-terminal)*	4.38	5.71	43.78	Impaired fertility – female
Dilatation of lumen in uterus (Continuous dose-terminal)*	4.38	5.71	43.78	Impaired fertility – female
Increased paired ovarian primordial follicle count (**F0**)	87.5	0.06	875.5	No monetisable effect correlate
Reduced epididymal sperm concentration (**F1**)**	87.5	-0.02	875.5	Impaired fertility – male offspring
Reduced daily sperm production/testis (**F3**)**	87.5	-0.02	875.5	Impaired fertility – male offspring
Increased gestational length (F0 and **F1**)	50.0	0.003	600	Reduced foetal growth/low birth rate
Decreased mean pup body weight/litter-PND-21-male (**F1**)	50.0	-0.03	600	No monetisable effect correlate
Decreased mean pup body weight/litter-PND-21-female (**F1**)	50.0	-0.03	600	No monetisable effect correlate
Note: *These effects are considered together. **These effects reflect the same underlying change and are therefore considered together.				

X11.3 Relevant sectors, uses, and operations

X11.3.1 Overview of the relevant sectors, uses, and operations/activities

This section provides an overview of the relevant sectors, uses and activities in which occupational exposure to BPA can be expected to occur.

BPA is a high-volume chemical with a multitude of end uses. BPA is predominantly used as an intermediate. It is REACH-registered in the tonnage band over 1,000,000 tonnes per annum.

According to PlasticsEurope (undated)[455], the European production volume of BPA was 1,150,000 tonnes in 2015, of which 73% was used in polycarbonate, 26% in epoxy resins and 1% in other uses.

The sectors and uses where occupational exposure can potentially take place are listed below.

Table X11-4: BPA – sectors, subsectors and uses/activities		
Sector	**Subsector**	**Uses/activities**
Chemicals sector	Manufacture of BPA	
	Manufacture of polycarbonate (PC)	
	Manufacture of epoxy resins and moderated epoxy resins (ER)	
	Manufacture of PVC (anti-oxidant for processing of PVC)	
	Manufacture of tin-plating additive	
	Manufacture of tetrabrominated flame retardants	
Paints & varnishes	Manufacture of liquid epoxy paints, lacquers and powder coatings, also adhesives (ER)	
Paper	Manufacture of thermal paper	
Manufacture of articles from PC and ER	Glass	Safety glass (glassy polymers) (PC) Spectacles (PC)
	Food contact materials	Containers (PC) Microwave-proof crockery (PC) Cooking utensils (PC) Drinks and food cans (EP)
	Automotive	Car parts, including transparent plastics (PC) Motorcycle helmets (PC)
	Electrical & electronic goods	Housing of devices, e.g. mobile phones, computers (PC) Optical storage media (PC) Circuit boards
	Building & construction	Plugs and switches (PC) Floorings (ER) Inner coatings for tanks and pipes (ER)
	Consumer goods	Composite materials (surfing boards and tennis rackets) (ER)
	Medical & healthcare	Medical equipment (PC) Dental sealing/fillings
Use of articles	Use of thermal paper	Shop receipts, public transport and parking tickets, fax messages
	Use of epoxy resin-based powder coatings, paints and lacquers	
	Use of other end products	
Laboratories	Use as laboratory reagent	
Sources: PlasticsEurope ECHA, https://echa.europa.eu/-/seven-new-substances-added-to-the-candidate-list-entry-for-bisphenol-a-updated-to-reflect-its-endocrine-disrupting-properties-for-the-environment EU RAR (2008) Ribeiro et al (2017) Subsport (2013): https://www.subsport.eu/wp-content/uploads/data/bisphenol_A.pdf		

The relevant uses/end products are summarised below for polycarbonate and epoxy resins.

[455] PlasticsEurope (undated), available at http://www.bisphenol-a-europe.org/wp-content/uploads/2017/07/Production-and-demand-volumes.pdf

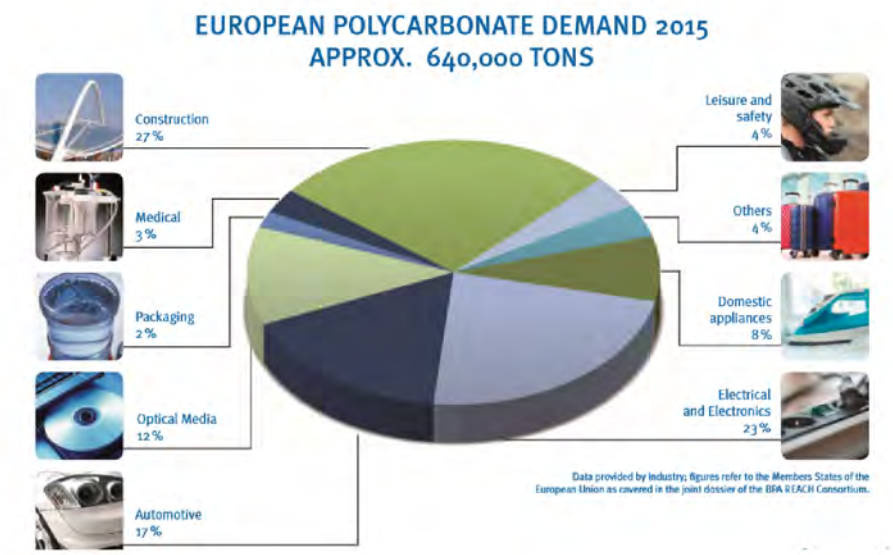


Figure X11-2: European use of polycarbonate, Source: PlasticsEurope, http://www.bisphenol-a-europe.org/wp-content/uploads/2017/07/Production-and-demand-volumes.pdf

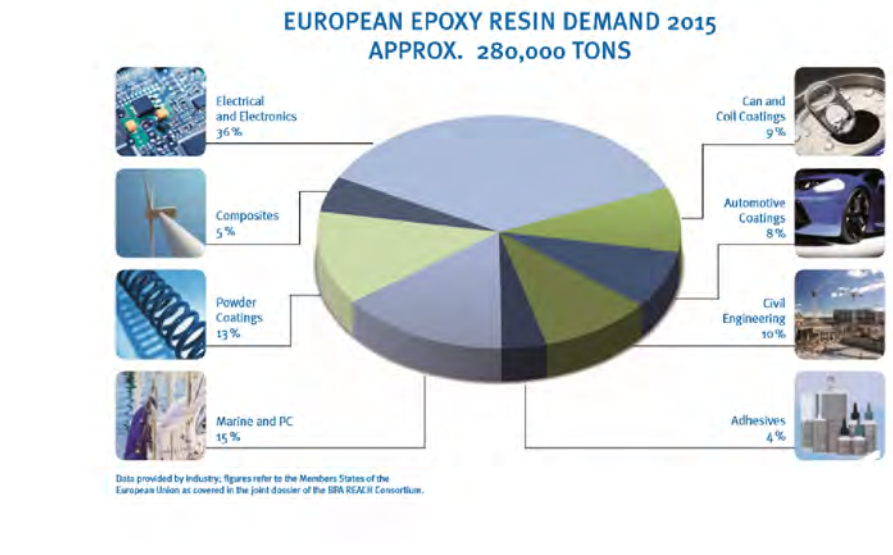


Figure X11-3: European use of epoxy resins, Source: PlasticsEurope, http://www.bisphenol-a-europe.org/wp-content/uploads/2017/07/Production-and-demand-volumes.pdf

X11.3.2 Thermal paper production and use

Traditionally, one of the key sectors of occupational exposure has been the production[456] and use of thermal paper. However, from 2 January 2020, BPA can no longer be used in thermal paper in the EU[457].

A market survey carried out by ECHA (2018) suggests that EU paper manufacturers have started to substitute BPA with BPS but the volume of BPS used remains relatively limited. According to ECHA (2018)[458]:

> *The substitution of BPA by BPS is worrisome given that ECHA's Risk Assessment Committee in its opinion on BPA indicated that BPS "is suspected to have many of the same adverse health effects as BPA."*

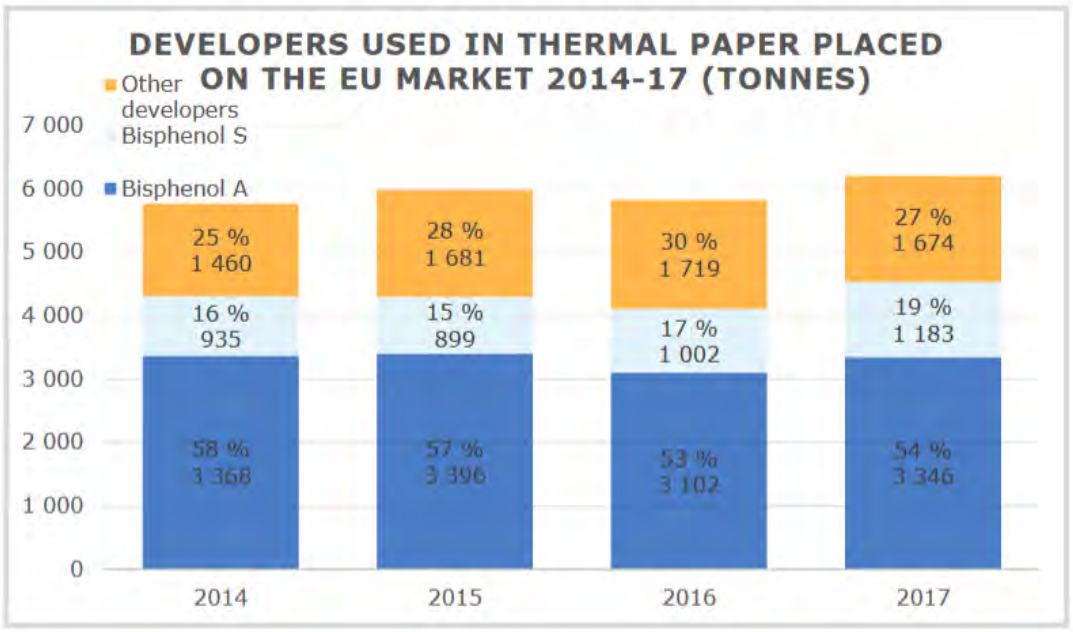


Figure X11-4: Developers used in thermal paper placed on the EU market, Source: ECHA (2018) https://echa.europa.eu/documents/10162/22863068/bpa_in_thermal_paper_report_en.pdf/0d93cd76-345e-2ed4-698f-a3beaea6d755

[456] About 30 % of thermal paper used in the EU is imported from China, India, Japan, Korea and the US, suggesting that 70% is placed on the EU market by EU manufacturers. Source: https://echa.europa.eu/-/bpa-being-replaced-by-bps-in-thermal-paper-echa-survey-finds. Thermal paper manufacturers in the EU include ETPA (European Thermal Paper Association) members, and Ricoh Industrie SAS (France), Blumberg GmbH & CoKG (Germany), Smith and McLaurin Ltd (UK). Source: https://echa.europa.eu/documents/10162/22863068/bpa_in_thermal_paper_report_en.pdf/0d93cd76-345e-2ed4-698f-a3beaea6d755

[457] Commission Regulation (EU) 2016/2235 concerning the restriction of bisphenol A in thermal paper will enter into force on 2 January 2020.

[458] https://echa.europa.eu/-/bpa-being-replaced-by-bps-in-thermal-paper-echa-survey-finds

Table X11-5: Developers used in thermal paper placed on the EU market by EU manufacturers in 2016 and 2017 (tonnes)			
Developer	**2016**	**2017**	**Change**
Bisphenol A	2 606	2 776	+7 %
Bisphenol S	200	397	+98 %
Other developers	1 065	1 022	-4 %
Total	3 871	4 195	+8 %
Source: European Thermal Paper Association (ETPA) quoted in ECHA (2018), https://echa.europa.eu/-/bpa-being-replaced-by-bps-in-thermal-paper-echa-survey-finds			

Table X11-6: Thermal paper placed on the EU market by EU manufacturers, 2014-17 (tonnes).					
Developer	**2014**	**2015**	**2016**	**2017**	**Change 2016-2017**
Bisphenol A	208,466	208,652	191,025	204,378	7%
Bisphenol S	11,682	11,106	15,035	34,010	126%
Other developers	73,938	89,865	93,688	89,860	-4%
Total	294,086	309,622	299,748	328,248	10%
Source: European Thermal Paper Association (ETPA) quoted in ECHA (2018), https://echa.europa.eu/-/bpa-being-replaced-by-bps-in-thermal-paper-echa-survey-finds					

For the purposes of this study, it is assumed that BPA in thermal paper will be substituted by 2020 and the use of BPA in thermal paper and occupational exposure from the printing of receipts is not considered in this report. In the absence of specific information on the substances that are likely to substitute BPA, no impacts of a potential 'regrettable substitution'[459] are assessed in this study.

X11.4 Exposed workforce

No estimates of the number of workers exposed (or potentially exposed) to BPA in the EU have been identified from published literature.

The EU Risk Assessment Report (EU RAR, 2008) notes that

> *"the total number of persons occupationally exposed to BPA is not known, but due to its widespread use in epoxy resins and polycarbonate it is expected to be thousands. However, the exposure is likely to be negligible in many cases as the residual BPA in epoxy resins and polycarbonate is low."*

With regard to the socio-economic contribution of Bisphenol A, PlasticsEurope (not dated a)[460] notes that, in 2010, 535,000 jobs in the EU depended, either directly or indirectly, on the production and use of polycarbonate. However, this estimate relates to the socio-economic contribution of BPA to one of its use sectors rather than to the number of workers exposed to BPA in the workplace.

Table X11-7: Employment directly or indirectly related to BPA		
Member State	**Sector**	**No of workers**
Belgium	Polycarbonate	15,300 linked to the production and consumption of PC 3,800 in the production industry, about 1,000 in processing, and 10,500 in the manufacturing and sale of end products are linked directly and indirectly to PC

[459] https://www.hbm4eu.eu/the-substances/bisphenols/

[460] http://www.bisphenol-a-europe.org/socio-economic-contribution/

Table X11-7: Employment directly or indirectly related to BPA		
Member State	**Sector**	**No of workers**
Czech Republic	Polycarbonate	No PC production, nearly 13,000 linked to the use of PC
Germany	Polycarbonate	Major producer of PC (40% of total European production) Almost 120,000 linked to the production and consumption of PC 8,000 in the production industry, 8,000 in processing, and 104,000 in manufacturing and sale of end products are linked directly and indirectly to PC in unique applications
Denmark	Polycarbonate	No PC production, 8,000 linked to the use of PC
Spain	Polycarbonate	Major producer of PC (20% of European production), 4,000 in the production industry, 2,000+ in processing, and 32,000 in manufacturing and sale of end products are linked directly and indirectly to PC in unique applications Total: 38,000
France	Polycarbonate	No PC production, 50,000 linked to the use of PC
Italy	Polycarbonate	No PC production, 46,000 linked to the use of PC
The Netherlands	Polycarbonate	Major producer of PC (20% of European production), 21,000 in the Netherlands are linked to the production and consumption of PC 4,200 in the production industry, 1,200 in processing, and 15,800 in manufacturing and sale of end products are linked directly and indirectly to PC in unique applications
Poland	Polycarbonate	No PC production, 22,000 linked to the use of PC
Sweden	Polycarbonate	No PC production, 13,000 linked to the use of PC
UK	Polycarbonate	No PC production, 98,000 linked to the use of PC
Source: PlasticsEurope (not dated a), http://www.bisphenol-a-europe.org/socio-economic-contribution/		

The exposed workforce has been estimated for the purposes of this study as shown below.

Table X11-8: BPA – Potentially exposed workers			
Sector	**Subsector/uses**	**Exposed workers**	**Details**
Chemicals sector	Manufacture of BPA	A: 1,000	Estimate: 4 companies with a total of 6 sites
	Manufacture of polycarbonate (PC)	B1: 80,000 B2: 20,000	5% of C22.2: Manufacture of plastic products DE: 40% capacity & 8,000 jobs NL: 20% capacity & 4,000 jobs
	Manufacture of epoxy resins and moderated epoxy resins (ER)	C: Included under B	
	Manufacture of PVC (anti-oxidant for processing of PVC)	D: Included under A	
	Manufacture of tin-plating additive	E: <1,000	Expected to be negligible
	Manufacture of tetrabrominated flame retardants (TBBA)	F: <1,000	Expected to be negligible

Table X11-8: BPA – Potentially exposed workers			
Sector	**Subsector/uses**	**Exposed workers**	**Details**
Paints & varnishes	Manufacture of liquid epoxy paints, lacquers and powder coatings, also adhesives (ER)	G: 7,500	5% of C20.3
Paper	Manufacture of thermal paper	H: Not estimated	Restriction from 2020
Manufacture of articles from PC and ER	Glass	I-O: 500,000	Estimate of socio-economic contribution taken as a proxy
	Food contact materials		
	Automotive		
	Electrical & electronic goods		
	Building & construction		
	Consumer goods		
	Medical & healthcare		
Use of articles	Use of thermal paper (shop receipts, etc.)	P: Not estimated	Restriction from 2020
	Use of epoxy resin-based powder coatings, paints and lacquers	Q: Not estimated	Exposure concentrations expected to be very low
	Use of other end products	R: Not estimated	
Laboratories	Use as laboratory reagent	S: Not estimated	

It is estimated that around 600,000 people in Europe work in jobs where there is a potential of occupational exposure to BPA.

X11.4.1 Breakdown by gender and age

The breakdown of the (potentially) exposed workforce by gender is provided below.

Table X11-9: BPA – potentially exposed workforce broken down by gender & age					
Sector	**Subsector/uses**	**Total exposed workers**	**% male**	**% female of reproductive age**	**M/F reproductive age**
Chemicals sector	Manufacture of BPA	A: 1,000	69%	23%	690/230
	Manufacture of polycarbonate (PC)	B1: 80,000 B2: 20,000	69%	23%	55,000/18,000 14,000/5,000
	Manufacture of epoxy resins and moderated epoxy resins (ER)	C: Included under B			
	Manufacture of PVC (anti-oxidant for processing of PVC)	D: Included under A			
	Manufacture of tin-plating additive	E: <1,000	69%	23%	690/230
	Manufacture of tetrabrominated flame retardants (TBBA)	F: <1,000	69%	23%	690/230
Paints & varnishes	Manufacture of liquid epoxy paints, lacquers and powder coatings, also adhesives (ER)	G: 7,500	69%	23%	5,000/2,000
Paper	Manufacture of thermal paper	H: Not estimated			
Manufacture of articles from PC and ER		I-O: 500,000	69%	23%	345,000/115,000
Use of articles	Use of thermal paper (shop receipts, etc.)	P: Not estimated			

Table X11-9: BPA – potentially exposed workforce broken down by gender & age					
Sector	Subsector/uses	Total exposed workers	% male	% female of reproductive age	M/F reproductive age
	Use of epoxy resin-based powder coatings, paints and lacquers	Q: Not estimated			
	Use of other end products	R: Not estimated			
Laboratories	Use as laboratory reagent	S: Not estimated			

X11.4.2 Trends

It is expected that all exposure to BPA in the production and use of thermal paper will cease in 2020.

PlasticsEurope (not dated a) notes that the consumption of polycarbonate in Germany and the UK has been growing by about 4% per annum. This value is taken as a proxy for potential future trends across the whole workforce exposed to BPA. It is therefore assumed that the number of workers exposed to BPA will increase at a rate of 4% per annum.

X11.4.3 Exposed workers: conclusion

The total number of potentially exposed workers is summarised below.

Table X11-10: Potentially exposed workforce: conclusion			
Estimate	No of exposed workers	Men of reproductive age	Women of reproductive age
Central estimate	600,000	410,000	140,000
Annual rate of change	4%	4%	4%

X11.5 Exposure levels

X11.5.1 Exposure routes

The key routes of occupational exposure differ by sector/use but generally include inhalation and dermal uptake.

The Clarity-BPA Programme (2018) notes that, whilst inhalation and dermal contact are the primary routes of exposure, intake estimates suggesting that inhalation was the more dominant exposure route.[461] Hines et al (2018)[462] also note that exposure to BPA can be dermal, oral and respiratory but in the manufacturing sector inhalation is dominant. This conclusion is based on an analysis of air and urine samples in six US companies that make BPA or products with BPA.

On the other hand, on the basis of an examination of exposure to BPA in six companies in Finland, Heinala et al (2017) note that "l*ow air levels, even in the companies with high urinary levels, suggest exposure via dermal contact.* […] *Since skin exposure is of potential concern in these tasks,*

[461] See https://ntp.niehs.nih.gov/results/areas/bpa/index.html

[462] Hines et al (2018): An Evaluation of the Relationship among Urine, Air, and Hand Measures of Exposure to Bisphenol A (BPA) in US Manufacturing Workers, https://academic.oup.com/annweh/advance-article-abstract/doi/10.1093/annweh/wxy042/5037158?redirectedFrom=fulltext

biomonitoring is recommended as the method for assessing occupational exposure to bisphenol A." However, Heinala et al (2017) also note that *"recommendations for more effective personal protection resulted in decreased exposure, particularly among coating machine operators"* in companies where urinary Bisphenol A levels were above the range seen in the general population.

With regard to till receipts, dermal exposure is the key route (Ndaw et al, 2016[463]; Ribeiro et al, 2017[464]); however, as noted above, exposure to BPA from dermal receipts will cease in 2020 in the EU and, as a result, it is not considered in this study.

All estimates of reproductive effects from BPA exposure in this study rely on inhalation thresholds and Dose-Response Relationships. Although there is no consensus about the dominant route of exposure:

- BPA is a skin sensitiser and workers are likely to already take precautions against dermal exposure (although it should be noted that it is also a respiratory sensitiser); and
- Where inhalation equivalents of urinary BPA levels can be estimated from available literature, these do not change the conclusions in terms of the industry sectors where impacts are expected to occur.

X11.5.2 Current exposure levels

Literature review

The following recent studies with exposure data have been identified: EU RAR (2008), Heinala et al (2017), Hines et al (2018), Kouidhi et al (2017) [465], and Ribeiro et al (2017).

The table below summarises the results from Heinala et al (2017)[466]:

Table X11-11: Exposure to Bisphenol A in Finland (Heinala et al, 2017)

Sector/use	Country	Study	Air concentration	Urine	Serum
Paint factory (liquid and powder paints) - 2 companies	Finland	Heinala et al (2017)[467]	Typically low (<40 µg/m3), except in some short-term duties related to the handling of solid bisphenol A	Production of liquid paint hardener post-shift up to 100-170 µg/l-1	
Composite product factory	Finland	Heinala et al (2017)		Similar to general population	

[463] Ndaw et al (2016): Occupational exposure of cashiers to Bisphenol A via thermal paper: urinary biomonitoring study, https://www.ncbi.nlm.nih.gov/pubmed/27126703

[464] Ribeiro et al (2017): Occupational Exposure to Bisphenol A (BPA): A Reality That Still Needs to be Unveiled, In: Toxics. 2017 Sep; 5(3): 22, available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5634705/pdf/toxics-05-00022.pdf

[465] Koudhi et al (2017): Occupational exposure to bisphenol A (BPA) in a plastic injection molding factory in Malaysia, https://pdfs.semanticscholar.org/d09d/1f5850d1554bd5e6e2245d974f1ac8281e20.pdf

[466] Heinala et al (2017): Assessment of Occupational Exposure to Bisphenol A in Five Different Production Companies in Finland, Annals of Work exposure Health 61:1, abstract available at https://www.ncbi.nlm.nih.gov/pubmed/28395312

[467] Heinala et al (2017): Assessment of Occupational Exposure to Bisphenol A in Five Different Production Companies in Finland, Annals of Work exposure Health 61:1, abstract available at https://www.ncbi.nlm.nih.gov/pubmed/28395312

Table X11-11: Exposure to Bisphenol A in Finland (Heinala et al, 2017)					
Sector/use	**Country**	**Study**	**Air concentration**	**Urine**	**Serum**
Thermal paper	Finland	Heinala et al (2017)	(maximum 17.6 mg/m3)	Production of coating material and operating coating machines Post-shift up to 130-250 µg/l-1 Highest: 1,000-1,500 µg/l-1	
Tractor factory	Finland	Heinala et al (2017)		Similar to general population	

The exposure scenarios reported in EU RAR (2008)[468] are summarised below.

Table X11-12: Exposure to Bisphenol A in the EU (EU RAR, 2008)					
Sector/use	**Country**	**Study**	**Air concentration (8hr TWA)**	**Air concentration – short-term**	**Dermal**
BPA manufacture	Not specified	EU RAR (2008)	8hr TWA ranging from none detected to 23.3 mg/m3 Reasonable worst case (90th percentile) 8 hr TWA 5 mg/m3	Short term ranging from none detected to 43.6 mg/m3 but generally rarely exceeds 10 mg/m3	Reasonable worst case 5mg/cm2/day
Polycarbonate manufacture	Not specified	EU RAR (2008)	Reasonable worst case 0.001 mg/m3 but charging of vessels reasonable worst case 0.7 mg/m3	Reasonable worst case 11 mg/m3	
PVC manufacture – Likely phased out	Not specified	EU RAR (2008)	Reasonable worst case 0.1 mg/m3	Reasonable worst case 1 mg/m3	
Manufacture of epoxy resins	Not specified	EU RAR (2008)	Not significant	Not significant	

[468] Please note that RIVM (2015) argues that the exposure scenarios in the EU RAR (2008) need to be recalculated "since current handling and risk reduction measures may differ from those in use when the EU RAR". Source: https://rivm.openrepository.com/rivm/bitstream/10029/600660/3/2015-0192.pdf

Table X11-12: Exposure to Bisphenol A in the EU (EU RAR, 2008)					
Sector/use	**Country**	**Study**	**Air concentration (8hr TWA)**	**Air concentration – short-term**	**Dermal**
Use of epoxy-resin based paints	Not specified	EU RAR (2008)	Reasonable worst case 0.01 mg/m3 or 0.5 mg/m3 for spraying coating powders and 0.0005 mg/m3 for dip-painting	Reasonable worst case 0.3 mg/m3	
Manufacture of thermal papers	Not specified	EU RAR (2008)	Reasonable worst case 0.1 mg/m3	Reasonable worst case 4 mg/m3	
Manufacture of plating additives	Not specified	EU RAR (2008)	Reasonable worst case 0.05 mg/m3		
Manufacture of TBBA flame retardant	Not specified	EU RAR (2008)	Estimate up to 0.000015 mg/m3		

Exposure estimates reported in other studies are given below (as cited in Ribeiro et al, 2017).

Table X11-13: Exposure to Bisphenol A in studies reviewed in Ribeiro et al (2017)					
Sector/use	**Country**	**Study**	**Air concentration**	**Urine**	**Serum**
Workplace plastics		Vandenberg et al (2007) cited in Ribeiro et al (2017)	208 ng/m3		
BPA manufacture & epoxy resin	China	He et al (2009) cited in Ribeiro et al (2017)	51 µg/m3	440–543 µg/g Cr (urine)	
BPA manufacture	China	Xiao et al (2009) cited in Ribeiro et al (2017)			102 µg/L (serum)
BPA manufacture & epoxy resin	China	Li et al (2010) cited in Ribeiro et al (2017)	2-15 µg/m3	58 µg/g Cr (urine)	
BPA manufacture & epoxy resin	China	Miaio et al (2011), cited in Ribeiro et al (2017)		9-28 µg/g Cr (urine)	
BPA manufacture & epoxy resin	China	Miaio et al (2011a), cited in Ribeiro et al (2017)		11 µg/g Cr (urine)	
Epoxy resin	China	Hang et al (2012), cited in Ribeiro et al (2017)		32±4 µg/g Cr (urine)	

Table X11-13: Exposure to Bisphenol A in studies reviewed in Ribeiro et al (2017)					
Sector/use	**Country**	**Study**	**Air concentration**	**Urine**	**Serum**
BPA manufacture	China	Miaio et al (2014), cited in Ribeiro et al (2017)		36 µg/g Cr (urine)	
BPA manufacture & epoxy resin	China	Liu et al (2015), cited in Ribeiro et al (2017)		686 µg/g Cr (urine)	
Epoxy resin	China	Miaio et al (2015), cited in Ribeiro et al (2017)		22 µg/g Cr (urine)	
Epoxy resin	China	Miaio et al (2014), cited in Ribeiro et al (2017)			19 ng/mL (serum)
BPA manufacture & epoxy resin	USA	Hines et al (2017)[469]		1-18,900 µg/g Cr, geometric mean 88.0 µg/g Cr	
BPA manufacture	Malaysia	Kouidhi et al (2017), cited in Ribeiro et al (2017)		4 ng/mL (urine)	
Liquid paint hardener Thermal paper	Finland	Heinala et al (2017), cited in Ribeiro et al (2017)		Median urinary BPA post-shift 100-170 µg/L (manufacturing liquid paint hardener urine workers) 130-250 µg/L (thermal paper manufacturing urine workers)	
Polycarbonate moulding plant	Taiwan	Chao et al (2015) cited in Ribeiro et al (2017)	32-50 µg/m3		

Conclusion

The data given in the preceding section are summarised in the table below. Most exposure appears to be below the thresholds for effects for BPA, with the exception of BPA manufacturing facilities, where the EU RAR (2008) estimated a reasonable worst-case scenario of 8hr TWAs 5 mg/m^3.

[469] Hines et al (2018): An Evaluation of the Relationship among Urine, Air, and Hand Measures of Exposure to Bisphenol A (BPA) in US Manufacturing Workers, https://academic.oup.com/annweh/advance-article-abstract/doi/10.1093/annweh/wxy042/5037158?redirectedFrom=fulltext

Table X11-14: BPA – Summary of data on workplace air concentrations (8-hr TWA mg/m3)					
Sector	**Subsector/uses**	**Total exposed workers**	**Typical/AM/GM**	**90th/95th percentile**	**Low-High Range**
Chemicals sector	Manufacture of BPA	A: 1,000	China: 0.05 mg/m3 China: 0.002-0.015 mg/m3	Reasonable worst case (90th percentile) 5 mg/m3	None-detected to 23.3 mg/m3
	Manufacture of polycarbonate (PC)	B1: 80,000 B2: 20,000		0.001 mg/m3 but charging of vessels reasonable worst case 0.7 mg/m3	
	Manufacture of epoxy resins and moderated epoxy resins (ER)	C: Included under B		Not significant	
	Manufacture of PVC (anti-oxidant for processing of PVC)	D: Included under A		Reasonable worst case 0.1 mg/m3	
	Manufacture of tin-plating additive	E: <1,000		Reasonable worst case 0.05 mg/m3	
	Manufacture of tetrabrominated flame retardants (TBBA)	F: <1,000		Estimate up to 0.000015 mg/m3	
Paints & varnishes	Manufacture of liquid epoxy paints, lacquers and powder coatings, also adhesives (ER)	G: 7,500		Reasonable worst case 0.01 mg/m3 or 0.5 mg/m3 for spraying coating powders and 0.0005 mg/m3 for dip-painting	
Paper	Manufacture of thermal paper	H: Not estimated	Consultation for this study: Several hundreds fold higher exposures than background levels EU RAR (2018): Reasonable worst case 0.1 mg/m3		
Manufacture of articles from PC and ER		I-O: 500,000	EU RAR (2008): However, the exposure is likely to be negligible in many cases as the residual BPA in epoxy resins and polycarbonate is low. EU RAR: 8hr TWAs rarely exceeded 5 mg/m3 in BPA manufacturing facilities and rarely exceeded 0.5 mg/m3 in other industries. Taiwan: 0.03-0.05 mg/m3		
Use of articles	Use of thermal paper (shop receipts, etc.)	P: Not estimated	Consultation for this study: not so much higher than background exposure of population		

Table X11-14: BPA – Summary of data on workplace air concentrations (8-hr TWA mg/m3)					
Sector	**Subsector/uses**	**Total exposed workers**	**Typical/AM/GM**	**90th/95th percentile**	**Low-High Range**
	Use of epoxy resin-based powder coatings, paints and lacquers	Q: Not estimated			
	Use of other end products	R: Not estimated			
Laboratories	Use as laboratory reagent	S: Not estimated			

It should be noted that the disadvantage of the approach focussing on air concentrations is that the potential bioaccumulation of BPA is not taken into account. According to Ribeiro et al (2017), whilst BPA average levels in occupational studies range from 10ng/mL to 100 ng/mL urine, median BPA concentration in serum is 27 ng/mL for workers exposed over 5 years and 10 ng/mL for workers exposed for less than 5 years.

X11.5.3 Estimation of an inhalation equivalent of inhalation and dermal uptake from urinary BPA levels

We compared a number of sources to (coarsely) correlate worker exposure to BPA. Very few data points on occupational BPA exposure exist and the available estimates vary widely. Please note that in one of studies the median and mean exposure (measure) values differ by a factor of 400, indicating the data are anything but normally distributed. We tried to calculate average exposures based on BPA urine levels expressed per unit creatinine. These estimates were either in the same (rough) neighbourhood or off by an order of magnitude or more. We have used the geometric mean or median here to estimate the exposure with the mean for the highly variable studies as our high estimate.

On average, ***BPA calculations (inhalation equivalent) based on the low average creatinine levels seem to range between 7 and 23 µg/m³ TWA_8 equivalent*** with massive excursions and non-normally distributed data as evidenced by the disparity between mean and median average data.

Estimate of BPA exposure in factory workers 1

The study was investigated to assess occupational exposure to bisphenol A in Finland[470]. Exposure was assessed by measuring total bisphenol A excretion (free and conjugated) from urine samples, and its concentrations in the air. The results revealed median concentrations of the post-shift urine samples of coating machine workers were in the range of 130-250 µg/l in thermal paper manufacturing. Estimates of air monitoring were "generally < 40 µg/m³". Considering this an estimate of BPA exposure in manufacturing can be calculated as follows:

STEP-1: BPA concentration in urine

Min: 130 µg/l	Max: 250 µg/l
Geomean:	180 µg/l

STEP-2: Estimate of total urine volume/day

[470] Heinälä M, Ylinen K, Tuomi T, Santonen T, Porras SP. Assessment of occupational exposure to Bisphenol A in five different production companies in Finland. Annals of work exposures and health. 2017 Jan 1;61(1):44-55. https://academic.oup.com/annweh/article-abstract/61/1/44/2762732

Considering a range of urinary output of 800-2000 ml/day for humans, a geometric mean of 1,265 ml/day can be calculated

Min:800 ml	Max: 2000 ml
Geomean:	1265 ml

STEP-3: Estimate of total daily intake of BPA

Assuming roughly that all BPA is excreted in 24 hrs (best guestimate[471]),

Urine (ml)	BPA excreted (µg/l)
1000	180
1265	228

Assuming 100% BPA excretion/day; Total daily intake of BPA = 228 µg (0.228 mg) (range 104-500 µg/day) which is equal to **0.003257 mg/kg bw/day** (0.228/70) or **0.0228 mg/m³** (0.228/10; factor 10 m^3 has been used for inhalation volume per shift). This correlates well with the study data estimate of average BPA exposure of < 40 µg/m^3 (excursions up to 17.6 mg/m^3!), especially given ***the range of 10-50 µg/m³ of our 23 µg/m³ estimate.*** This type of concordance is an exception for these estimates.

Worker Exposure 2

He et al. investigated occupational exposure levels of BPA among Chinese workers and measured BPA levels in workplaces and urine BPA levels of workers: TWA_8 concentrations of airborne BPA in factories was 450 µg/m^3 (Mean) and 6.67 µg/m^3 (Median)[472].

They also reported **urinary BPA concentrations** of workers occupationally exposed to BPA as below:

Pre-shift: 4630 µg/g Cr (Mean) and 84.6 µg/g Cr (Median) and Post-shift: 5400 µg/g Cr (Mean) and 111 µg/g Cr (Median).

Conversion of urinary BPA µg/g Cr into µg/L:

Normal values of Creatinine = 0.5- 1.5 mg/dl of Urine.[473]

1L Urine is equivalent to 5-15 mg creatinine or conversely 5-15 mg creatinine is equivalent to 1 L urine. So, 1000 mg (or 1 g) Creatinine is equivalent to 66.7-200 L Urine

"x" µg of a substance/g Cr = x µg of substance/66.7 L urine (when creatinine level is on the higher side); or conversely "x" µg of a substance/g Cr = x µg of substance/200 L urine (when creatinine level

[471] This is an overestimate as BPA concentrations slowly build up day to day including over days off.

[472] He Y, Miao M, Wu C, Yuan W, Gao E, Zhou Z, Li DK. Occupational exposure levels of bisphenol A among Chinese workers. Journal of occupational health. 2009;51(5):432-6. https://www.jstage.jst.go.jp/article/joh/51/5/51_O9006/_pdf/-char/en

[473] Source: http://www.scymed.com/en/smnxps/psxdf212_c.htm

is on the lower side); or "x" µg of a substance/g Cr = x µg of substance/100 L urine (when creatinine level is at the median)

Therefore, using the above calculation procedure one gets the following results for BPA urine concentrations in µg/L[474].

Table X11-15: BPA urine concentrations				
For median	**Level in µg/g Cr**	**Level in µg/L(lower Cr.)**	**Level in µg/L(higher Cr.)**	**Level in µg/L(median Cr.)**
Pre-shift	84.6	0.42	1.27	0.85
Post-shift	111	0.56	1.66	1.11

Estimate of total urine volume/day

Considering urinary output of 800-2000 ml/day for humans, a Geometric mean of 1265 ml/day can be calculated

Min: 800 mL	Max: 2000 mL
Geomean:	1265 mL

Estimate of total daily intake of BPA

Assuming roughly that all BPA is excreted in 24 hrs (working estimate), and therefore, the same volume is considered as exposed to/inhaled/consumed per day.

[474] The very conservative assumption is made here that post shift concentration reflects shift exposure (which we know may not be the case at higher concentrations of BPA)

Table X11-16: Occupational threshold and dose-response				
		BPA level (µg/L)	total BPA excreted (µg/day)	
For mean	Pre-shift	23.2	29.3	Low Cr. Level
	Post-shift	27.0	34.2	
	Pre-shift	69.4	87.8	High Cr. Level
	Post-shift	81.0	102	
	Pre-shift	46.3	58.6	Median Cr. Level
	Post-shift	54.0	68.3	
For median	Pre-shift	0.42	0.53	Low Cr. Level
	Post-shift	0.56	0.71	
	Pre-shift	1.27	1.61	High Cr. Level
	Post-shift	1.66	2.10	
	Pre-shift	0.85	1.08	Median Cr. Level
	Post-shift	1.11	1.40	

Total BPA Exposure concentrations

Table X11-17: BPA concentrations					
	BPA in exposed workers (µg/day)	BPA in unexposed workers (µg/day)	after background deduction (µg/day)	Total BPA concentration in blood (µg/L)[475]	final BPA exposure (µg/m³)
For mean (lower Cr. Level)					
Pre-shift	29.3	0	29.3	4.88	2.93
Post-shift	34.2	0	34.2	5.69	3.42
For mean (higher Cr. Level)					
Pre-shift	87.8	0	87.8	14.6	8.78
Post-shift	102	0	102	17.1	10.2
For mean (median Cr. Level)					
Pre-shift	58.6	0	58.6	9.76	5.86
Post-shift	68.3	0	68.3	11.4	6.83
For median (lower Cr. Level)					
Pre-shift	0.53	0	0.53	0.09	0.05
Post-shift	0.71	0	0.71	0.12	0.07
For median (higher Cr. Level)					
Pre-shift	1.61	0	1.61	0.27	0.16
Post-shift	2.10	0	2.10	0.35	0.21
For median (median Cr. Level)					
Pre-shift	1.08	0	1.08	0.18	0.11
Post-shift	1.40	0	1.40	0.23	0.14

Given that air concentrations were measured at 7 – 450 µg/m³ (unclear whether this is a mean with excursions or a general range, although stated as mean and median value respectively) the creatinine method seems to considerably underestimate the BPA concentration unless one uses the mean estimate for the exposure concentrations which may be true given that it looks like some serious outliers affect the mean (similar to study 1 above). If excursions on the order of 100-fold do occur then correlating the BPA urine/creatinine data with median exposure levels might prove quite adequate. Otherwise one is looking at a 1.5- to two-fold order of difference between results. One theory is that excursions in airborne exposure also would be associated with prolonged dermal exposure but this

[475] Assuming average volume of blood to be 6 L.

appears unsupported by these data. Background (preshift) BPA levels seem to indicate incomplete clearance of BPA from the body which would indicate even lower levels of exposure. Concordance between these numbers is thus nigh on non-existent. Urinary BPA levels thus may not be the best measure of BPA exposure as measured here.

TWA_8 concentrations of airborne BPA in factories (µg/m³)
Mean: 450
Median: 6.67

Worker Exposure 3

Another study studied the semen quality of the workers exposed to the bisphenol A (BPA)[476]. Twenty BPA exposed and 16 control workers with similar age, physical activities were included in the study. Tests included quantifying BPA in blood samples and investigating the quantity and quality of semen. In 94.4% of the exposed workers median BPA level was found to be 101.94 µg /L and in only 18.8% control subjects BPA was found: the median level of BPA was 0 µg /L. The sperm density of exposed workers [(68.65 +/- 44.00) x 10(6)/ml] was significantly lower than that of control [(118.56 +/- 98.36) x 10(6)/ml].

At 6 litres of blood and a BPA concentration of 101.94 µg/L, the BPA exposure is as follows

BPA in exposed workers (µg/day)	BPA in unexposed workers (µg/day)	After background deduction (µg/day)		Final BPA exposure (µg/m3)
611.64	0	611.64		**61.16**

With this exposure concentration of 0.061 mg/m³, we calculated the slope as -690.11.

- Converted (mg/m³) 0.061
- Response (%) -42.09682861
- Slope -690.1119444
- Units of slope %/mg/m³

X11.6 Market analysis

There are four manufactures in the EU with six sites. These are given in the table below.

Table X11-18: Manufacturers of BPA		
Sector	**Company**	**Production facilities**
BPA manufacture	Coverstro (previously Bayer Material Science)	Antwerp (Belgium) Krefeld (Germany)
	Dow Chemical	Stade (Germany)
	Hexion (Momentive Specialty Chemicals)	Pernis (The Netherlands)
	SABIC Innovative Plastics	Bergen op Zoom (The Netherlands) Cartagena, Spain

[476] Xiao GB, Wang RY, Cai YZ, He GH, Zhou ZJ. Effect of bisphenol A on semen quality of exposed workers: a pilot study. Zhonghua lao dong wei sheng zhi ye bing za zhi= Zhonghua laodong weisheng zhiyebing zazhi= Chinese journal of industrial hygiene and occupational diseases. 2009 Dec;27(12):741-3 (abstract)

Table X11-18: Manufacturers of BPA		
Sector	Company	Production facilities
Sources: EUR RAR (2008), ICIS (2011): https://www.icis.com/resources/news/2011/05/09/9457899/european-chemical-profile-bisphenol-a/		

The socio-economic characteristics of the sectors in which BPA exposure may occur are summarised below.

- C17 - Manufacture of paper and paper products
- C20.1 Manufacture of basic chemicals, fertilisers and nitrogen compounds, plastics and synthetic rubber in primary forms
- C20.3 - Manufacture of paints, varnishes and similar coatings, printing ink and mastics
- C22.2: Manufacture of plastic products
- C23.1 - Manufacture of glass and glass products
- C26: Manufacture of computer, electronic and optical products
- F41 - Construction of buildings
- Q86 - Human health activities

X11.6.1 Number of SMEs in each sector

Table X11-19: Number and proportion of SMEs by size of enterprise and sector									
Sector	TOTAL	Micro		Small		Medium		Large	
	No. firms	No. firms	% of total	No. firms	% of total	No. firms	% of total	No. firms	% of total
C17	**19,580**	12,630	65%	4,490	23%	1,980	10%	490	3%
C20.1	**8,980**	5,190	58%	2,010	22%	980	11%	360	4%
C20.3	**3,910**	2,280	58%	1,080	28%	430	11%	120	3%
C22.2	**54,220**	35,490	65%	13,050	24%	4,900	9%	780	1%
C23.1	**15,340**	12,490	81%	1,920	13%	690	4%	240	2%
C26	**40,440**	30,230	75%	7,000	17%	2,510	6%	700	2%
F41	**870,000**	820,300	94%	43,400	5%	5,100	1%	470	0.1%
Q86	**12,650**	-	-	-	-	-	-	-	-
Source: Eurostat's Structural Business Statistics database									

X11.6.2 Average turnover by size of enterprise

Table X11-20: Average turnover by sector and size of enterprise, 2016												
Sector	Micro			Small			Medium			Large		
	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m
C17	4,923	12,630	0.39	18,166	4,490	4.05	60,980	1,980	30.80	102,610	490	209.41
C20.1	6,854	5,190	1.32	19,422	2,010	9.66	68,909	980	70.32	234,358	360	650.99
C20.3	1,138	2,280	0.50	5,176	1,080	4.79	13,846	430	32.20	20,843	120	173.69
C22.2	11,410	35,490	0.32	46,395	13,050	3.56	98,462	4,900	20.09	78,698	780	100.89

Table X11-20: Average turnover by sector and size of enterprise, 2016												
Sector	Micro			Small			Medium			Large		
	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m
C23.1	1,984	12,490	0.16	4,186	1,920	2.18	11,432	690	16.57	29,135	240	121.40
C26	11,316	30,230	0.37	24,040	7,000	3.43	51,321	2,510	20.45	200,000	700	285.71
F41	-	820,300	-	-	43,400	-	-	5,100	-	-	470	-
Q86	-	-	-	-	-	-	-	-	-	-	-	-
Source: Eurostat's Structural Business Statistics database												

X11.6.3 R&D expenditure

Table X11-21: Business expenditure on R&D per sector (in € million), EU28		
Sector	Data availability	R&D expenditure (in €m)
C17	C17	372.9
C20.1	C20	6,659.7
C20.3	C20	6,659.7
C22.2	C22	2,371
C23.1	C23	881.7
C26	C26	16,732
F41	F	F: 839.8
Q86	Q86	370.2
Source: Eurostat Notes: EU28 totals do not include data for some member states, due to confidentiality.		

X11.7 Burden of ill health

X11.7.1 Summary of the assessment framework

Overview of monetisable effects and toxicological/epidemiological endpoints

The monetisable effects considered in this study are summarised below, together with the corresponding effects for which no-effect thresholds and DRR have been estimated.

Table X11-22: BPA – summary of health effects					
Monetisable effect	Health effect	Outcome – Fer/Dev		Cause - Exposed workers	
		Fer	Dev	F	M
Impaired fertility – male offspring	Decreased seminal vesicle weight in F1 males		F1m	F	M
	Reduced epididymal sperm concentration (**F1**)	F0m	F0m	F	M
	Reduced daily sperm production/testis (**F3**)		F1m	F	M
	Increased gestational length (F0 and **F1**)*	F0f	F1f	F	
Impaired fertility – male &	Decrease in mean # pups	F0fm		F	M
	Decrease in mean # litters/pair	F0fm		F	M

Table X11-22: BPA – summary of health effects					
Monetisable effect	Health effect	Outcome – Fer/Dev		Cause - Exposed workers	
		Fer	Dev	F	M
Impaired fertility - female					
Impaired fertility – male	Decreased epididymal sperm concentration (**F0**)	F0m			M
Impaired fertility – female	Epithelial hyperplasia (Vagina) (Continuous dose-terminal)**	F0f		F	
	Dilatation of lumen in uterus (Continuous dose-terminal)**	F0f		F	
	Increased gestational length (F0 and **F1**)	F0f	F1f	F	M
Spontaneous abortion/still-birth	Decrease in # of live pups/litter	F0f		F	
	Decrease in # of live pups	F0f		F	
Reduced foetal growth/low birth rat	Increase in cumulative days to litter	F0fm		F	M
Note: *Attributed to monetisable effect 'Impaired fertility – male offspring' since corresponding monetary value for impaired fertility of female offspring is not available. ** Considered together					

X11.7.2 Screening of relevant sectors

Comparing the exposure data in with the no effect thresholds shows that the only sector where exposure data shows exceedance of any threshold is BPA manufacturing where the reasonable worst-case scenario suggests exposure at 5 mg/m3 8-hr TWA which exceeds the lower of the thresholds for impaired fertility – female (4.38 mg/m3 8-hr TWA). Assuming exposure at the average OEL of the countries where BPA manufacturing facilities are based (7.5 mg/m3 8-hr TWA) leads to the same conclusion; no thresholds are exceeded with the exception of 4.38 mg/m3 8-hr TWA for 'impaired fertility – female' are exceeded.

Two scenarios have been estimated:

- Scenario A: Workers in BPA manufacturing exposed at 5 mg/m3
- Scenario B: Workers in BPA manufacturing exposed at the average OEL of the Member States with BPA production facilities (7.5 mg/m3)

Both scenarios are calculated for female workers only with the key effect being 'impaired female fertility'. The two effects for which exposure exceeds the thresholds under the scenarios modelled in this study and the relevant DRRs are summarised below, together with the expected % change at the two scenarios. Both of these effects are relevant to 'impaired fertility – female'.

Table X11-23: BPA – effects used for estimation					
Monetisable effect	Effect	Threshold	DRR	Scenario 1: % change at 5 mg/m3	Scenario 2: % change at 7.5 mg/m3
Impaired fertility - female	Epithelial hyperplasia (Vagina) (Continuous dose-terminal)	4.38	y=5.71x-25.0098	3.5%	17.8%
	Dilatation of lumen in uterus (Continuous dose-terminal)	4.38	y=5.71x-25.0098	3.5%	17.8%

However, the result for epithelial hyperplasia of the vagina is not seen as a distinct effect that can be translated to the monetisable effect separately from dilatation of lumen in uterus. Therefore, only 'dilatation of lumen in uterus' is considered further in this assessment.

X11.7.3 Cases of ill health

In the case of 'dilatation of lumen in uterus' it is expected that a % change estimated using the DRR equals the additional fraction of female workers of reproductive age that suffer from 'impaired fertility. This is because in the Clarity NTP BPA (2018) study dilatation of lumen in uterus is a histopathological change which is associated with a disruption of normal female menstrual cycle and thus equated with 'impaired fertility' for the purposes of this study. Scenarios A and B are summarised below.

Table X11-24: BPA – effects used for estimation – Scenarios A and B

Effect	Effect	Threshold	DRR	Exposed workers	Concentration	Cases
Impaired fertility – female	Dilatation of lumen in uterus (Continuous dose-terminal)	4.38	y=5.71x-25.0098	230	Scenario A: 5 mg/m3	3.5% of 230 = 8 cases
					Scenario B: 7.5 mg/m3	17.8% of 230 = 41

X11.8 Future developments under the baseline scenario

An increase in the number of workers can be expected. Assuming that then increase is at the same rate as the recent increases in the numbers of workers involved in the production of polycarbonate, an increase of around 4% per annum can be expected. However, further reductions in exposure concentrations can also expected due to the recent lowering of the indicative OELV under the CAD to 2 mg/m^3 which is under the thresholds for effects considered in this report. Exposure reduction to the level of the new IOELV would reduce the number of cases calculated in this report to 0.

Annex 12 Borates

X12.1 Introduction

X12.1.1 Relevant substances

Boron is a trace element present as borate minerals within Earth's crust. Boron exposure in humans occurs mainly through food and drinking water. Boron compounds in the presence of water are transformed into borates. In biological systems, nearly 96% of the boron is present as boric acid, $B(OH)_3$ and as a small amount of borate anion, $B(OH)_4$. Other inorganic borates convert to boric acid at physiological pH prior to absorption and more than 90% of administered doses of inorganic borates are excreted in the urine as boric acid. For the inhalation route, in a conservative or worst case scenario, 100% absorption of boric acid is assumed.

Several boron compounds are included in this analysis (boric acid, disodium tetraborate, diboron trioxide, perboric acid or sodium salts, and disodium octaborate) and their effects are analysed, mainly on reproduction and development in animals and humans. Based on their metabolism and conversion at or under physiological conditions, they are assumed to all act through boric acid or the borate anion. Hence their effects are discussed here together regardless of their original chemical form. Boron, the pure element, does exist and gets used in small quantities in alloys and metallurgical compounds. It does not at act or behave in a similar manner to borates and is therefore excluded from this analysis.

In addition, all oral exposure data from animal studies, where applicable, were converted into inhalation exposure data (see section X12.1.6 and below). Occupational exposure is generally quantified/regulated as inhalation exposure. Where dermal exposure does play a significant role, it is easily controlled through industrial hygiene control measures such as protective clothing and handwear.

To unify the results, all borates are converted to boron equivalents throughout the analysis using the equivalents in Table X12-1 below.

Table X12-1: Borate reprotoxins –list of borate compounds included and their characteristics

Characteristic	Diboron trioxide	Disodium tetraborate	Boric acid	Perboric acid, sodium salt	Disodium octaborate
EC Number	215-125-8	215-540-4	233-139-2	234-390-0	234-541-0
CAS Number	1303-86-2	1303-96-4 1330-43-4 12179-04-3	10043-35-3	10332-33-9 11138-47-9 12040-72-1 37244-98-7	12008-41-2 12280-03-4
Name and alternative names	Diboron trioxide (boron oxide, boron sesquioxide, boric oxide, boria, boric acid anhydride)	Disodium tetraborate, decahydrate (borax, sodium borate, sodium tetraborate, decahydrate) Disodium tetraborate, anhydrous	Boric acid	Perboric acid, sodium salt (sodium perborate anhydrous) Perboric acid, sodium salt (sodium	Disodium octaborate (Disodium octaborate anhydrate, boron sodium oxide) Disodium octaborate tetrahydrate

Table X12-1: Borate reprotoxins –list of borate compounds included and their characteristics					
Characteristic	**Diboron trioxide**	**Disodium tetraborate**	**Boric acid**	**Perboric acid, sodium salt**	**Disodium octaborate**
		(borax anhydrous, borax glass, sodium tetraborate, anhydrous) Disodium tetraborate, pentahydrate (borax pentahydrate)		perborate monohydrate) Perboric acid, sodium salt, trihydrate (sodium perborate trihydrate) Perboric acid, sodium salt, tetrahydrate (sodium perborate tetrahydrate)	
Chemical formula	B_2O_3	$Na_2B_4O_7 \cdot 10H_2O$ $Na_2B_4O_7$ $Na_2B_4O_7 \cdot 5H_2O$	BH_3O_3	$BH_3O_4.Na$ $BHO_3.H_2O.Na$ $BH_3O_4.3H_2O.Na$ $BHO_3.4H_2O.Na$	$B_8Na_2O_{13}$ $Na_2B_8O_{13}.4H_2O$
Molecular weight	69.62	381.38 201.22 291.35	61.83	99.81 99.81 153.9 153.9	153.86 412.53
Boron content %	31.06	11.34 21.49 14.85	17.48	10.83 10.83 7.02 7.02	25.40 20.96
Source: RPA research and Verisk3E					

X12.1.2 Hazard classification

Borates classification is harmonised under annex VI of regulation (EC) No 1272/2008 (CLP regulation), as Repr 1B, with perboric acid, sodium salt also classified as Acute Tox. 4. Details of this classification, along with other notified classification and labelling, according to CLP criteria, are listed in Table X12-2.

Table X12-2: Borate reprotoxins – hazard classifications					
Characteristic	**Diboron trioxide**	**Disodium tetraborate**	**Boric acid**	**Perboric acid, sodium salt**	**Disodium octaborate**
CAS Number	1303-86-2	1303-96-4 1330-43-4 12179-04-3	10043-35-3	10332-33-9 11138-47-9 12040-72-1 37244-98-7	12008-41-2 12280-03-4
Class type	CLH	CLH	CLH	CLH	CLH
Hazard Class and Category Code(s)	R1B	R1B	R1B	Ox. Sol. 3 Repr. 1B Acute Tox. 3 * Acute Tox. 4 * STOT SE 3 Eye Dam. 1	R1B
Hazard Statement Code(s)	H360Df	H360Df	H360Df	H272 H302 H318 H331 H335 H360Df	H360Df
Specific conc limit	>= 3.1%	>= 4.5% >= 8.5% >= 6.5%	>= 5.5%	H360D >=6.5< 9% H360Df >= 9%	≥ 0.3%
Pictograms Signal Word Code(s)	GHS08 Dgr	GHS08 Dgr	GHS08 Dgr	GHS03 GHS05 GHS06 GHS08 Dgr	GHS08 Dgr
Tonnes per year (REACH)	1,000 – 10,000	100,000 – 1, 000,000	100,000 – 1,000,000.	10,000 – 100,000	1,000 – 10,000
Candidate list (REACH)	Y	Y	Y	Y	Y

Source: Table 3.1, List of harmonised classification and labelling of hazardous substances, CLP Regulation No 1272/2008 https://eur-lex.europa.eu/legal-content/en/TXT/PDF/?uri=CELEX:02008R1272-20180301&from=EN

Notes

H360Df = May damage fertility and the unborn child
H319: Causes serious eye irritation
H318: Causes serious eye damage
H272: May intensify fire; oxidiser
H331: Toxic if inhaled
H302: Harmful if swallowed
H335: May cause respiratory irritation

X12.1.3 Existing OELs and BLVs

The Swedish authorities seek to reduce the borates specific concentration limits (SCLs) from their values in Table X12-3 and have submitted a (harmonised classification and labelling) CLH note in the registry of intentions. It is assumed that they wish to reduce them to the reprotoxins R1B default value of 0.3%.

The known occupational exposure limits (OELs) for borates in the EU and in selected third countries are also given in Table X12-3. No biological limit values (BLVs) could be found for any member states or for the EU.

Table X12-3: Borate reprotoxins and their OELs in Member States and some third countries							
Member State	Diboron trioxide (boron oxide)	Disodium tetraborate, anhydrous	Disodium tetraborate, decahydrate	Disodium tetraborate, pentahydrate	Boric acid	Perboric acid, sodium salt	Disodium octaborate
	CAS 1303-86-2 EC 215-125-8	CAS 1330-43-4 EC 215-540-4	CAS 1303-96-4 EC 215-540-4	CAS 12179-04-3 EC 215-540-4	CAS 10043-35-3 EC 233-139-2	CAS 10332-33-9, 11138-47-9, 12040-72-1*, 37244-98-7* EC 234-390-0	CAS 12008-41-2, 12280-03-4 EC 234-541-0
	mg/m^3	mg/m^3	mg/m^3	mg/m^3	mg/m^3	mg/m^3	mg/m^3
AT	15						
BE	10	2	2	2	2		
BG	5						
CY							
CZ							
DE		5 (1)	5 (2)	5 (3)	10 (4)		
DK	10	1	2	1	5		
EE			2				
EL	15	10	10	10			
ES	10	2	2	2	2		
FI	10	0.5	0.5	0.5	0.5	0.5	0.5
FR	10	1	5	1	5		
HR	10	1	5	1			
HU (7)	>=3.1%	>=4.5%	>=8.5%	>=6.5%	>=5.5%		
IE	10	1	5	1			
IT	10	2	2	2	2	2 (6)	2
LT		1	2	1	10		
LV	5				10	1 (6)	
LX							
MT							
NL					5	1 (5)	
PL	10		0.5			4	
PT	10	2	2	2	2		
RO	10						

Table X12-3: Borate reprotoxins and their OELs in Member States and some third countries							
Member State	Diboron trioxide (boron oxide)	Disodium tetraborate, anhydrous	Disodium tetraborate, decahydrate	Disodium tetraborate, pentahydrate	Boric acid	Perboric acid, sodium salt	Disodium octaborate
	CAS 1303-86-2 EC 215-125-8	CAS 1330-43-4 EC 215-540-4	CAS 1303-96-4 EC 215-540-4	CAS 12179-04-3 EC 215-540-4	CAS 10043-35-3 EC 233-139-2	CAS 10332-33-9, 11138-47-9, 12040-72-1*, 37244-98-7* EC 234-390-0	CAS 12008-41-2, 12280-03-4 EC 234-541-0
	mg/m^3	mg/m^3	mg/m^3	mg/m^3	mg/m^3	mg/m^3	mg/m^3
SE			2		5		
SI							
SK							
UK	10	1	5	1	5		
Range	5 - 15	0.5 - 10	0.5 - 10	0.5 - 10	0.5 - 10	0.5 - 4	0.5 - 2
Mean	10	1.9	3.0	2.3	4.8	1.7 (8)	1.3
Median	10	1.0	2.0	1.0	2.0	1.0	1.3
Mode	10	1.0	2.0	1.0	2.0	1.0	-
DNEL	4.7	6.7	6.7	6.7	8.3	0.062	6.9
Third countries							
CH	10 (1)				1.8 (1)		
TR							
AU		1	5	1	5		
IL							
JP							
NZ	10		5	1			
SG		1	5	1			
SKR	10	1	5	1			
CN							
CAN					2		

Table X12-3: Borate reprotoxins and their OELs in Member States and some third countries							
Member State	Diboron trioxide (boron oxide)	Disodium tetraborate, anhydrous	Disodium tetraborate, decahydrate	Disodium tetraborate, pentahydrate	Boric acid	Perboric acid, sodium salt	Disodium octaborate
	CAS 1303-86-2 EC 215-125-8	CAS 1330-43-4 EC 215-540-4	CAS 1303-96-4 EC 215-540-4	CAS 12179-04-3 EC 215-540-4	CAS 10043-35-3 EC 233-139-2	CAS 10332-33-9, 11138-47-9, 12040-72-1*, 37244-98-7* EC 234-390-0	CAS 12008-41-2, 12280-03-4 EC 234-541-0
	mg/m^3	mg/m^3	mg/m^3	mg/m^3	mg/m^3	mg/m^3	mg/m^3
USA (ACGIH)					2		
USA (OSHA)					5		

Source: RPA research and various others including Etimine USA Inc, Safety Data Sheet for boric acid http://www.etimineusa.com/sites/etimineusa.com/files/SDS%20-%20Boric%20Acid%202016%20-%202018.pdf

Notes

** These CAS numbers have no associated OELs are included for completeness*

1 Advisory, inhalable aerosol

2 Advisory, inhalable aerosol: calculated as boron

3 Advisory, inhalable aerosol, calculated as boron: 0.75mg/m³

4 Advisory, inhalable fraction, calculated as boron: 1.8 mg/m³

5 SML specific migration limit mg/kg

6 Only for CAS 10332-33-9

7 All Hungary's values are specific concentration limits

8 Mean for 10332-33-9 is 17mg/m^3, for 11138-47-9 is 18 mg/m^3

X12.1.4 DNELs (Derived No Effect Levels)

Pure boron has a relatively high DNEL[477] of 97.95 mg/m^3 because is not absorbed or metabolized and passes straight through the body "without" effects. As explained earlier, it does not at act or behave in a similar manner to borates and is therefore excluded from this analysis.

The DNELs for the borate compounds considered in this study are given in Table X12-4.

Table X12-4: Borate reprotoxins – DNELs and assessment factors				
Population	**Exposure Route**	**DNEL (mg/m^3 * or mg/kg bw/day)**	**Overall assessment factor**	**Most sensitive endpoint**
Diboron trioxide (CAS Number: 1303-86-2) (2)				
Workers	Inhalation (Long term)	4.66 *	12.5	Developmental toxicity / teratogenicity
	Dermal (Long term)	220.6	30	Developmental toxicity / teratogenicity
General Population	Inhalation (Long term)	2.34	25	Developmental toxicity / teratogenicity
	Dermal (Long term)	110.3	60	Developmental toxicity / teratogenicity
	Oral (Long term)	0.55	60	Repeated dose toxicity
	Oral (Short term)	0.55	60	Developmental toxicity / teratogenicity
Disodium tetraborate (CAS Number: 1303-96-4, 1330-43-4, 12179-04-3) (3)				
Workers	Inhalation (Long term)	6.7 *	12.5	Repeated dose toxicity
	Dermal (Long term)	316.4	30	
General Population	Inhalation (Long term)	3.4 *	25	Developmental toxicity / teratogenicity
	Dermal (Long term)	159.5	60	Developmental toxicity / teratogenicity
	Oral (Long term)	0.79	60	Developmental toxicity / teratogenicity
	Oral (Short term)	0.79	60	Developmental toxicity / teratogenicity
Boric acid (CAS Number: 10043-35-3) (4)				
Workers	Inhalation (Long term)	8.3 *	12.5	Developmental toxicity / teratogenicity
	Dermal (Long term)	392	30	Developmental toxicity / teratogenicity
General Population	Inhalation (Long term)	4.15 *	25	Repeated dose toxicity
	Dermal (Long term)	196	60	Repeated dose toxicity
	Oral (Long term)	0.98	60	Repeated dose toxicity
	Oral (Short term)	0.98	60	Developmental toxicity / teratogenicity
Perboric acid Sodium salt (CAS Number: 10332-33-9, 11138-47-9, 12040-72-1, 37244-98-7) (5)				
Workers	Inhalation (Long term)	2 *	1	Irritation (respiratory tract)
	Dermal (Long term)	101	9	Repeated dose toxicity
	Dermal (Long term)	101	9	Repeated dose toxicity
General Population	Inhalation (Long term)	0.5 *	4	Irritation (respiratory tract)
	Dermal (Long term)	36	18	Repeated dose toxicity

[477] https://echa.europa.eu/registration-dossier/-/registered-dossier/14776/7/1

Table X12-4: Borate reprotoxins – DNELs and assessment factors				
Population	**Exposure Route**	**DNEL (mg/m³ * or mg/kg bw/day)**	**Overall assessment factor**	**Most sensitive endpoint**
	Oral (Long term)	0.36	1800	Repeated dose toxicity
Disodium octaborate tetrahydrate (Disodium octaborate) (CAS Number: 12280-03-4, 12008-41-2) (6)				
Workers	Inhalation (Long term)	6.9 *	12.5	Developmental toxicity / teratogenicity
	Dermal (Long term)	326	30	Developmental toxicity / teratogenicity
General Population	Inhalation (Long term)	3.5 *	25	Irritation (respiratory tract)
	Dermal (Long term)	163.3	60	Developmental toxicity / teratogenicity
	Oral (Long term)	0.81	60	Developmental toxicity / teratogenicity
	Oral (Short term)	0.81	60	Developmental toxicity / teratogenicity
Sources: ECHA registration dossiers *1 https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/14776/7/1* *2 https://echa.europa.eu/registration-dossier/-/registered-dossier/14790/7/1* *3 https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/15357/7/1* *4 https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/15472/7/1* *5 https://www.echa.europa.eu/hu/web/guest/registration-dossier/-/registered-dossier/13523/7/1* *6 https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/14136/7/1* *Notes * DNELs are in mg/m³, otherwise mg/kg bw/day*				

X12.1.5 Legislation other than CAD

There are no REACH restrictions on borates.

All of the five borate compounds being considered are on the candidate list: disodium octoborate was added in June 2018.

X12.1.6 Chemical safety reports

Detailed information about exposure levels and risk management measures (RMMs) was obtained from the chemical safety reports (CSRs). A single CSR is provided by one company on behalf of the borates industry for four of the borates compounds. A fifth CSR was provided for perboric acid, sodium salt by another company, but this did not include the attachment that covered human exposure.

The four CSRs gave detailed information about the exposure scenarios (ES). The CSRs for boric acid and disodium tetraborate, anhydrous were very similar, covering the same 41 ES. Comparing the two sets, a handful of differences in exposure levels were spotted: it isn't clear if these were intentional differences or caused by errors in cutting and pasting. It is much easier for the analysis if the compounds have the same exposure data and fortunately, even if the differences are intentional, they do not alter the conclusions.

The other two CSRs for diboron trioxide and disodium octaborate each covered a subset of the 41 ES, again with very similar exposure data.

X12.2 Summary of health endpoints, thresholds & DRRs

X12.2.1 Relevant reproductive health endpoints

Relevant reproductive health endpoints, identified from literature review, are summarised below, along with a monetised health effect that may be used to value it. The table only lists adverse effects which:

- are deemed as potentially relevant to humans (i.e. they have a potential for human effects correlation);
- have a no-effect threshold and dose response relationship (DRR) that could be derived; and
- have data which is derived from study that is clearly relevant to occupational exposure.

Relevant effects were grouped according to their effects on the reproductive system and embryonic/foetal development.

Table X12-5: Borate reprotoxins – effects that are relevant to humans and have a response

Effects seen	Fertility/ development?		Exposed workers	
	Fer	Dev	F	M
Decrease in mating index (1)	Fer			M
Decrease in fertility index (1)	Fer			M
Decrease in right testis weight (F0) (1)		Dev		M
Decrease in right caput and corpus epididymis (1)		Dev		M
Decrease in prostrate weight (F0) (1)		Dev		M
Decrease in right cauda epididymis weight in F0 males (1)		Dev	F	M
Decrease in foetal body weight/litter-male (GD20) (4)		Dev	F	M
Decrease in foetal body weight/litter-female (GD20) (4)		Dev	F	M
Increase in offspring with short rib XIII/litter (GD20) (4)		Dev	F	M
Decrease in foetal body weight/litter (3)		Dev	F	
Decrease in foetal body weight (3)		Dev	F	
Increase in malformed foetuses/litter (3)		Dev	F	
Increased % malformed foetuses/litter (external malformation) (3)		Dev	F	
Increased % malformed foetuses/litter (visceral malformation) (3)		Dev	F	
Increased % malformed foetuses/litter (skeletal malformation) (3)		Dev	F	
Increased % foetuses with cardiovascular malformations (3)		Dev	F	
Decrease in adjusted live pup weight (1)		Dev	F	M

Table X12-5: Borate reprotoxins – effects that are relevant to humans and have a response				
Effects seen	**Fertility/ development?**		**Exposed workers**	
	Fer	**Dev**	**F**	**M**
Sources: Verisk3E research and the following: *1 Fail PA, George JD, Seely JC, Grizzle TB, Heindel JJ. Reproductive toxicity of boric acid in Swiss (CD-1) mice: assessment using the continuous breeding protocol. Fundamental and Applied Toxicology. 1991 Aug 1;17(2):225-39.* *http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.872.9249&rep=rep1&type=pdf* *2 Heindel JJ, Price CJ, Schwetz BA (1994). The developmental toxicity of boric acid in mice, rats and rabbits. Environ Health Perspect 102(Suppl 7):107-112.* *https://scholar.google.co.in/scholar?hl=en&as_sdt=0%2C5&q=The+developmental+toxicity+of+boric+acid+in+mice%2C+rats+and+rabbits&btnG=* *3 Heindel JJ, Price CJ, Field EA, Marr MC, Myers CB, Morrissey RE, Schwetz BA. Developmental toxicity of boric acid in mice and rats. Toxicological Sciences. 1992 Feb 1;18(2):266-77. https://www.ncbi.nlm.nih.gov/pubmed/1601227* *Alternate reference for Mice study: Heindel JJ, Price CJ, Field EA, Marr MC, Myers CB, Morrissey RE & Schwetz BA. Developmental toxicity of boric acid in mice and rats. As cited in ECHA dossier boric acid: https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/15472/1* *Alternate reference for Rabbit study: ECHA Dossier for Boric acid. Unnamed report, 1991.* *4 Price CJ, Strong PL, Marr MC, Myers CB, Murray FJ. Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation. Toxicological Sciences. 1996 Aug 1;32(2):179-93* *https://scholar.google.co.in/scholar?hl=en&as_sdt=0%2C5&q=Developmental+toxicity+NOAEL+and+postnatal+recovery+in+rats+fed+boric+acid+during+gestation&btnG=*				

X12.2.2 Other health endpoints

Several maternal endpoints were also found and are given in Table X12-6. The thresholds for all except the "decreased mean body weight gain" are above highest exposure levels considered.

Table X12-6: Borate reprotoxins - maternal effects seen	
Effects seen	**Threshold dose (mg/ m^3) (no effects)**
Increase in right kidney weight (2)	23.33
Increased relative kidney weight (1)	43.51
Increased liver and kidney weights (1)	23.95
Decreased weight gain (1)	23.95
Decreased mean body weight gain (3)	12.25
Sources *1 Heindel JJ, Price CJ, Field EA, Marr MC, Myers CB, Morrissey RE, Schwetz BA. Developmental toxicity of boric acid in mice and rats. Toxicological Sciences. 1992 Feb 1;18(2):266-77. https://www.ncbi.nlm.nih.gov/pubmed/1601227* *Alternate reference for Mice study: Heindel JJ, Price CJ, Field EA, Marr MC, Myers CB, Morrissey RE & Schwetz BA. Developmental toxicity of boric acid in mice and rats. As cited in ECHA dossier boric acid* *https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/15472/1* *Alternate reference for Rabbit study: ECHA Dossier for Boric acid. Unnamed report, 1991.* *2 Price CJ, Strong PL, Marr MC, Myers CB, Murray FJ. Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation. Toxicological Sciences. 1996 Aug 1;32(2):179-93* *https://scholar.google.co.in/scholar?hl=en&as_sdt=0%2C5&q=Developmental+toxicity+NOAEL+and+postnatal+recovery+in+rats+fed+boric+acid+during+gestation&btnG=* *3 ECHA Registration Dossier for Perboric acid, sodium salt; 1995 Unnamed Study Report.* *https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/13523/7/9/2*	

X12.2.3 Summary of thresholds and DRRs

The threshold dose is the dose above which we can quantify effects, below this level effects are assumed to be similar to those at control (non occupational) exposure levels. The upper limit is the limit of the interval across which one can extrapolate the slope. Above this limit one should not use the slope identified here. The slope is the % increase over control value for each mg/m^3 of exposure. (A slope of 2%/mg/m^3 means that at 5 mg/m^3 ABOVE threshold the effect would increases 2 x 5=10%.) The slope is considered to hold constant between the threshold and upper limit.

In Table X12-7 there are five endpoints for increases in various malformed foetuses/litter. Four of these are removed because they are mutually exclusive and the trend analysis is the most appropriate and conservative choice given the range of concentrations and effects.

Figure X12-1 shows the dose response relationships for all the endpoints in Table X12-7 between the thresholds and upper limits. The upper limits for two endpoints are not shown to make the graph easier to understand: these are "Decrease in right cauda epididymis weight in F0 males" and "Increased % malformed foetuses/litter (skeletal malformation)". The value of the DNEL x 10 for boric acid converted to boron is also shown, because as will be discussed in section X12.5.2, this is the only exposure level considered that is higher than some of the thresholds.

Table X12-7: Borate reprotoxins - effects and dose response relationship – effects that are relevant to humans and have a response

Effects seen	Threshold dose mg/m3/kg/day (no effects)	Upper limit mg/ m^3	Slope %/mg/m^3	Monetisable effect correlate
Decrease in mating Index (1)	26.67	111.58	0.73 *	Impaired male fertility
Decrease in fertility Index (1)	26.67	111.58	1.10 *	Impaired male fertility
Decrease in right testis weight (F0) (1)	26.67	111.58	0.60 *	Impaired male fertility
Decrease in right caput and corpus epididymis (1)	26.67	111.58	0.25 *	Impaired male fertility
Decrease in prostrate weight (F0) (1)	26.67	111.58	0.23 *	Impaired male fertility
Decrease in right cauda epididymis weight in F0 males (1)	111.58	221.4	0.17 *	Impaired male fertility
Decrease in offspring body weight/litter-male (GD20) (4)	16.89	23.34	0.96 *	Reduced foetal growth
Decrease in offspring body weight/litter-female (GD20) (4)	16.89	23.34	1.10 *	Reduced foetal growth
Increase in offspring with short rib XIII/litter (GD20) (4)	22.72	44.52	0.18	Developmental abnormality
Decrease in foetal body weight/litter (2)	2.39	23.94	0.32 *	Reduced foetal growth
Decrease in foetal body weight (2)	43.51	79.3	0.31 *	Reduced foetal growth
Increased % malformed foetuses/litter (skeletal malformation) (2)	10.1	101.3	6.74	Developmental abnormality
Decrease in adjusted live pup weight (1)	26.67	111.58	0.17 *	Reduced foetal growth

Table X12-7: Borate reprotoxins - effects and dose response relationship – effects that are relevant to humans and have a response				
Effects seen	**Threshold dose mg/m3/kg/day (no effects)**	**Upper limit mg/ m^3**	**Slope %/mg/m^3**	**Monetisable effect correlate**
Sources: Verisk3E research and the following: *1 Fail PA, George JD, Seely JC, Grizzle TB, Heindel JJ. Reproductive toxicity of boric acid in Swiss (CD-1) mice: assessment using the continuous breeding protocol. Fundamental and Applied Toxicology. 1991 Aug 1;17(2):225-39.* *http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.872.9249&rep=rep1&type=pdf* *2 Heindel JJ, Price CJ, Schwetz BA (1994). The developmental toxicity of boric acid in mice, rats and rabbits. Environ Health Perspect 102(Suppl 7):107-112.* *https://scholar.google.co.in/scholar?hl=en&as_sdt=0%2C5&q=The+developmental+toxicity+of+boric+acid+in+mice%2C+rats+and+rabbits&btnG=* *3 Heindel JJ, Price CJ, Field EA, Marr MC, Myers CB, Morrissey RE, Schwetz BA. Developmental toxicity of boric acid in mice and rats. Toxicological Sciences. 1992 Feb 1;18(2):266-77.* *https://www.ncbi.nlm.nih.gov/pubmed/1601227 Alternate reference for Mice study: Heindel JJ, Price CJ, Field EA, Marr MC, Myers CB, Morrissey RE & Schwetz BA. Developmental toxicity of boric acid in mice and rats. As cited in ECHA dossier boric acid: https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/15472/7/9/3/?documentUUID=c43ab11a-d1bd-40c8-9080-db8524084f24* *Alternate reference for Rabbit study: ECHA Dossier for Boric acid. Unnamed report, 1991.* *4 Price CJ, Strong PL, Marr MC, Myers CB, Murray FJ. Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation. Toxicological Sciences. 1996 Aug 1;32(2):179-93* *https://scholar.google.co.in/scholar?hl=en&as_sdt=0%2C5&q=Developmental+toxicity+NOAEL+and+postnatal+recovery+in+rats+fed+boric+acid+during+gestation&btnG=* *Notes * Slope is made positive, but represents an effect that decreases as exposure increases*				

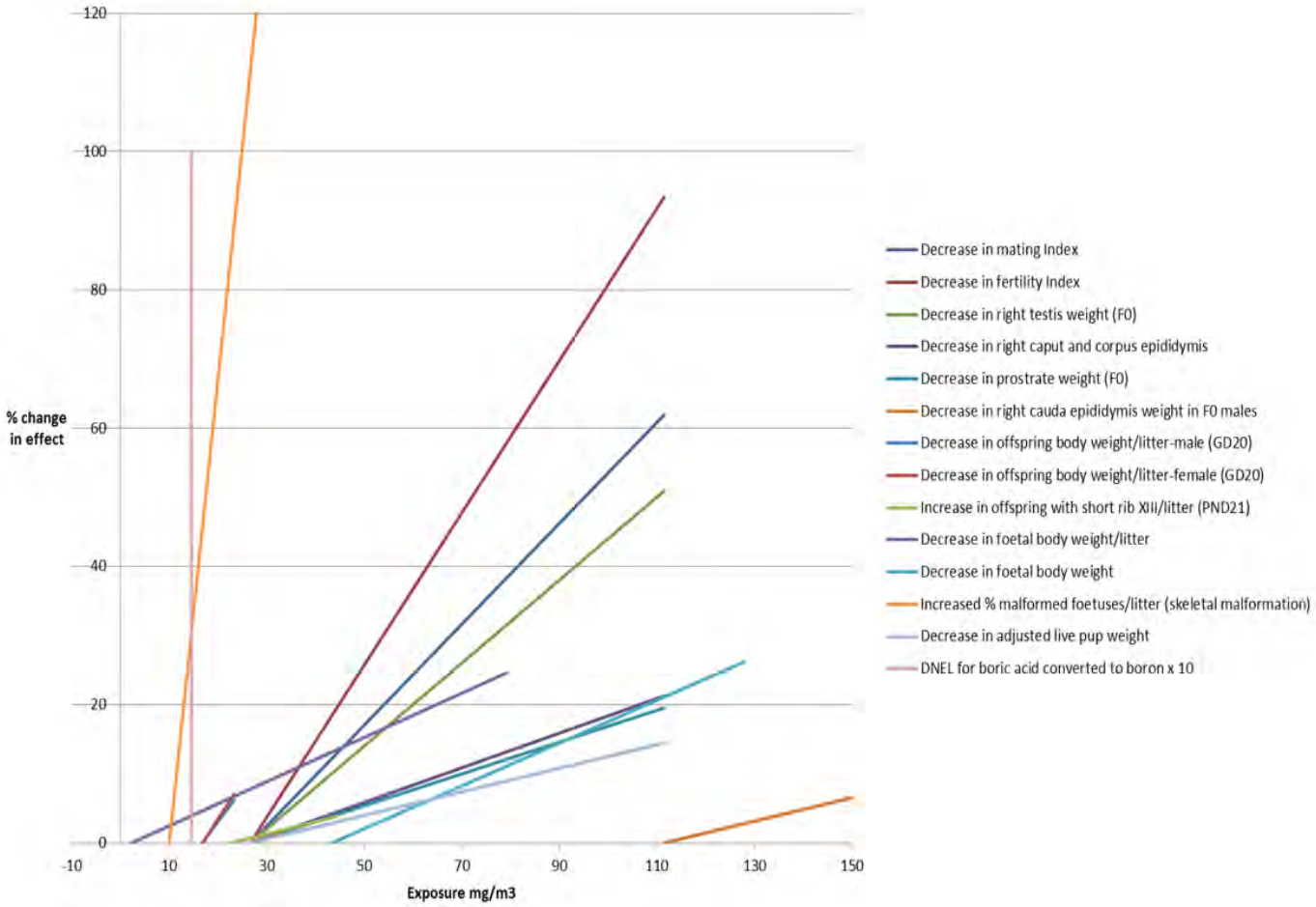


Figure X12-1: Dose response relationship for all possible effects, showing threshold, slope and upper limit
Source: RPA analysis
Notes: The upper limits for "Decrease in right cauda epididymis weight in F0 males" and "Increased % malformed foetuses/litter (skeletal malformation)" are not shown for clarity

X12.3 Relevant sectors, uses, and operations

X12.3.1 Introduction

The data about sectors using borates comes from three sources:

- REACH sector of use (SU)
- Data from the German MEGA exposure database[478]
- Data from the European Borates Association
- Data from the chemical safety reports (CSRs)

If one of these sources mentions the sector, then it is included in the analysis, see Table X12-8. The sectors using borates reflect the overall supply chain and fall into four sub groups:

1. Importers and wholesalers of borates, who are members of the European Borates Association (EBA)
2. Chemicals and glass industries, which is supplied directly by the EBA members
3. Manufacturing sectors many of which are supplied by the chemicals industry
4. Professional workers using the end products

In the CSRs, for 37 of the exposure scenarios the highest exposure levels are below the DNEL for boric acid converted to boron of 1.45mgB/m^3 (which is used the target DNEL throughout the CSRs). In the table, the column for CSRs indicates that there was evidence in the CSRs for one of the three scenarios:

- Y = Yes, all exposure levels in the CSRs below lowest threshold of 2.39mgB/m^3
- Y* = some exposure levels in the CSRs above 2.39 mg/ m3 and below 10mgB/m^3
- N = Not mentioned in the CSRs

There are four exposure scenarios whose range goes above the lowest threshold of 2.39mgB/m^3. These are:

- ES8 - Discharging big bags (750-1500kg) into mixing vessels
- ES15 - Off-loading borates from ships
- ES20 - Packaging into big bags (750-1500kg)
- ES21 - General maintenance activities

Table X12-8: Borate reprotoxins – sectors mentioned by REACH sectors of use, the MEGA exposure database and EBA, together with the sector sub group used in analysis

Sector & NACE code	MEGA	REACH SU	EBA	CSRs	Sector sub group
A Agriculture		Y		Y	4
B Mining		Y		N	(Note 1)
F Construction	Y	Y		Y	4
C10 Manufacture of food products		Y		N	3
C16 Manufacture of wood and of products of wood and cork, except furniture; manufacture of articles of straw and plaiting materials	Y	Y		N	4

[478] IFA MEGA evaluations: Boron and its compounds (2012) https://www.dguv.de/medien/ifa/en/fac/reach/mega_auswertungen/boron.pdf

Table X12-8: Borate reprotoxins – sectors mentioned by REACH sectors of use, the MEGA exposure database and EBA, together with the sector sub group used in analysis					
Sector & NACE code	**MEGA**	**REACH SU**	**EBA**	**CSRs**	**Sector sub group**
C17 Manufacture of paper and paper products		Y		Y*	4
C18 Printing and reproduction of recorded media		Y		Y*	4
C20 Manufacture of chemicals and chemical products	Y	Y	Y	Y*	2
C21 Manufacture of basic pharmaceutical products and pharmaceutical preparations			Y	Y*	3
C22 Manufacture of rubber products		Y		Y*	4
C23 Manufacture of other non-metallic mineral products (glass and ceramics)	Y	Y	Y	Y*	2
C24 Manufacture of basic metals	Y	Y		Y*	3
C25 Manufacture of fabricated metal products, except machinery and equipment	Y	Y	Y	Y*	3
C26 Manufacture of computer, electronic and optical products		Y		Y	3
C27 Manufacture of electrical equipment	Y	Y		Y	3
C28 Manufacture of machinery and equipment n.e.c.	Y	Y		Y*	3
C29 Manufacture of motor vehicles, trailers and semi-trailers	Y	Y		Y*	3
C30 Manufacture of other transport equipment	Y	Y		Y*	3
C31 Manufacture of furniture		Y		Y*	4
C35.1 Electric power generation, transmission and distribution		Y	Y	N	3
G46.77 Wholesale of waste and scrap	Y			N	3
H52.1 Wholesaling			Y	Y*	1
M72 Scientific research and development		Y		N	3
Q86 Human health activities		Y		N	4
Sources: REACH registration dossiers, MEGA exposure database, European Borates Association and RPA research *Notes: 1 – excluded as boron is not mined in the EU.*					

These sectors and the exposure levels that their workers are likely to experience are discussed below, to determine which sectors are analysed further.

X12.3.2 Sectors

Sub group 1 - Importers and wholesalers

The six members of the EBA are the importers and wholesalers of borates in Europe. Several of these companies responded to the consultation and they operate comprehensive risk management methods.

In the CSRs, two of the five exposure scenarios with high exposure levels apply to this sector and only to this sector:

- ES15 - Off-loading borates from ships
- ES20 - Packaging into big bags (750-1500kg)

Both of these scenarios have ranges that go up to 10mgB/m^3 and both have 90th percentile exposure values that are above the lowest threshold for ill health of 2.39mgB/m^3. However, there is a detailed description of the many sub scenarios that apply to these ES and these are the worst case exposure values. There is also a detailed description of the respiratory protective equipment (RPE) that workers are required to wear in situations when the exposure levels may rise above the DNEL of boric acid converted to boron of 1.45mgB/m^3. These processes are fundamental to these companies' business and they are well aware of the risk and their relatively small number of workers is likely to be well trained.

Therefore, the study team believe that the risk of exposure to high levels of borates by individual workers in this sub group is low. In Table X12-9, the wholesaling sector is the EBA members themselves (sub group 1).

Table X12-9: Borate reprotoxins – exposed workers and companies in wholesaling and importing sector

	Number
Number of exposed workers	400
Number of companies	6
Source: EBA	

Chemicals and glass industries

The sectors supplied by EBA members in 2017, together with the amount of borates provided in tonnes are shown in Table X12-10. This clearly shows that two sectors receive nearly 70% of all the borates imported into the EU:

- C20 Manufacture of chemicals and chemical products – 24.5% of the borates from EBA members go to this sector
- C23 Manufacture of other non-metallic mineral products (glass and ceramics) products – 69% of the borates from EBA members go to this sector

These sectors are included in the analysis of exposed workers and cases of ill health.

In the CSRs, two of the five exposure scenarios with high exposure levels apply to these sectors:

- ES8 - Discharging big bags (750-1500kg) into mixing vessels
- ES21 - General maintenance activities

Both of these scenarios have ranges that go up to approximately 10mgB/m^3 but both have 90th percentile exposure values that are below the lowest threshold for ill health of 2.39mgB/m^3; the 90th percentile exposure values for ES21 - General maintenance activities are below the DNEL for boric acid converted to boron on 1.45mgB/m^3.

Table X12-10: Borate reprotoxins – sectors supplied by EBA members and tonnages 2017			
Sector	**Notes (NACE codes, etc.)**	**Tonnes (average of 2015/16 data)**	**%**
C20 Manufacture of chemicals and chemical products			
Adhesives	C20.52 Manufacture of glues	2,758	0.7
Agriculture (fertilizers)	C20.1: Manufacture of basic chemicals, fertilisers and nitrogen compounds, plastics and synthetic rubber in primary forms	38,083	9.8
Analytical reagent	C20.59 Manufacture of other chemical products n.e.c.	470	0.1
Catalysts	C20.59 Manufacture of other chemical products n.e.c.	70	< 0.1
Chemical synthesis	C20: Manufacture of chemicals and chemical products	29,357	7.5
Coatings (formulation of paints and coatings)	C20.3: Manufacture of paints, varnishes and similar coatings, printing inks and mastics	3,933	1.0
Construction (wood preservation, flame retardants, formulation of borates in plaster board)	C20.3: Manufacture of paints, varnishes and similar coatings, printing inks and mastics Also in C23	2,389	0.6
Detergents	C20.4: Manufacture of soaps and detergents, cleaning and polishing preparations, perfumes and toilet preparations	8,245	2.1
Industrial fluids	C20.3 Manufacture of paints, varnishes and similar coatings, printing inks and mastics	9,812	2.5
Printing paper (PVA solutions)	C20.5 Manufacture of other chemical products n.e.c.	31	< 0.1
Total (C20 chemicals)		**95,148**	**24.5**
C23 Manufacture of other non-metallic mineral products (particularly glass and ceramics)			
Abrasives	C23.9 Manufacture of abrasive products and non-metallic mineral products n.e.c.	2,226	0.6
Cellulose insulation	C23.6 Manufacture of fibre cement C23.9 Manufacture of other non-metallic mineral products n.e.c.	9,895	2.5
Ceramics (production of frits)	C23.3 Manufacture of clay building materials C23.4 Manufacture of other porcelain and ceramic products	52,891	14
Construction (wood preservation, flame retardants, formulation of borates in plaster board)	C23.6 Manufacture of articles of concrete, cement and plaster Also in C20	2,389	0.6
Glass (production of glass wool, high alkali glass and low alkali glass)	C23 Manufacture of glass and glass products	197,469	51
Non-oxide Ceramics	C23.3 Manufacture of clay building materials C23.4 Manufacture of other porcelain and ceramic products	40	< 0.1
Refractories	C23.2 Manufacture of refractory products	770	0.2
Total (C23 Glass and ceramics)		**265,680**	**69**
Wholesaling (1)	**H52.1 Warehousing and storage**	**22,477**	**5.8**
Other			
Metallurgy	C25.6 Treatment and coating of metals	6,733	1.7

Table X12-10: Borate reprotoxins – sectors supplied by EBA members and tonnages 2017			
Sector	**Notes (NACE codes, etc.)**	**Tonnes (average of 2015/16 data)**	**%**
Nuclear applications	D35.1: Electricity power generation, transmission and distribution	750	0.2
Oil industry (formulation into cement)		62	< 0.1
Photography		81	< 0.1
Tablet Production and Use	C21 Manufacture of basic pharmaceutical products and pharmaceutical preparations	60	< 0.1
Total (other)		**7,686**	**2.2**
Total (all sectors)		**388,608**	**100**
Sources: European Borates Association and RPA research *Notes: 1 These are EBA members*			

Manufacturers using borate products

In Table X12-10, the "Other" sector only accounts for 2.2% of the borates directly supplied by importers and wholesalers and these uses are included in sub group 3, which are predominantly manufacturers. These manufacturers mainly use products supplied to them by the chemicals industry. Borates are used in the glass industry as intermediates and therefore borates are not present in the final product and there is no exposure to borates from users of products supplied by the glass/frit industries. The manufacturing sectors supplied with products containing borates by the chemicals industry are:

- C10: Manufacture of food products
- C21: Manufacture of basic pharmaceutical products and pharmaceutical preparations
- C24: Manufacture of basic metals
- C25: Manufacture of fabricated metal products, except machinery and equipment
- C26: Manufacture of computer, electronic and optical products
- C27 Manufacture of electrical equipment
- C28 Manufacture of machinery and equipment n.e.c.
- C29: Manufacture of motor vehicles, trailers and semi-trailers
- C30 Manufacture of other transport equipment
- C35.1 Electric power generation, transmission and distribution
- G38.1 Wholesale of waste and scrap
- M72 Scientific research and development

In the CSRs, C10, D35.1, E38.1 and M72 are not mentioned and the highest exposure levels for the exposure scenarios that apply to C26, C27 are below the lowest threshold of 2.39mgB/m^3. The remaining sectors all include two of the five exposure scenarios with higher exposure levels:

- ES8 - Discharging big bags (750-1500kg) into mixing vessels
- ES21 - General maintenance activities

Both of these scenarios have ranges that go up to 10mgB/m^3 but both have 90th percentile exposure values that are below the lowest threshold for ill health of 2.39mgB/m^3; the 90th percentile exposure values for ES21 - General maintenance activities are below the DNEL for boric acid converted to boron on 1.45mgB/m^3.

These manufacturers represent a huge group of workers, who are generally using products containing borates in the process of manufacturing other products. Often they only use the products for part of their working time and many are protected by risk management measures for other substances that they use. The products used by these sectors usually contain a low level of borates. Nonetheless, these sectors are included in the analysis to give a conservative view of exposed workers and cases of ill health.

Professional workers using end products

The professional workers using the end products include

- Agriculture – professional users of fertilisers (farmers).
- C16 Manufacture of wood and of products of wood and cork, except furniture; manufacture of articles of straw and plaiting materials
- C17 Manufacture of paper and paper products
- C18.1 Printing and service activities related to printing
- C22 Manufacture of rubber products
- C31 Manufacture of furniture
- F Construction - professional users of products such as cellulose and articles made of concrete, cement and plaster.
- Q86 Human health activities – relates to the use of soap and detergents by professional health care workers

This sub group employs vast numbers of workers. However, for a variety of reasons, none of these sectors is considered to be likely to have workers exposed to the levels of borates required to cause any ill effects. These reasons include:

- Occasional use, often only a few days a year (agriculture, construction)
- Risk management measures already used, often for other substances, and workers with a good understanding of dangers (agriculture, construction)
- Very low levels of exposure measured, see Table X12-11 (construction, wood)
- Very low level of borates in products used (human health activities, furniture, rubber and printing)
- Task are performed outdoors (agriculture, construction)

Table X12-11: Borate reprotoxins – sectors where professional workers use end products with borates		
Sector	**Employees**	**Enterprises**
A Agriculture – professional users of pesticides and fertilisers (farmers).	10,894,170	10,000,000
C16 Manufacture of wood and of products of wood and cork, except furniture; manufacture of articles of straw and plaiting materials	833,152	170,426
C17 Manufacture of paper and paper products	626,469	19,300
C18.1 Printing and service activities related to printing	608,642	110,000
C22 Manufacture of rubber products	1,622,461	61,928
C31 Manufacture of furniture	868,006	120,000
F Construction - professional users of products such as cellulose and articles made of concrete, cement and plaster.	9,759,919	3,409,660
Q86 Human health activities – relates to the use of soap and detergents by professional health care workers	NA	NA
Total, not including human health activities	**Approx 30 million**	**Approx 14 million**
Sources: Eurostat (online data: sbs_sc_ind_r2, ef_kvecsleg, RPA research		

X12.3.3 Uses

Table X12-12: Borate reprotoxins – uses within sectors	
Sector	**Notes (NACE codes, etc.)**
Chemicals and glass industries sub group	
C20 Manufacture of chemicals and chemical products	
Adhesives	C20.52 Manufacture of glues
Agriculture (fertilizers)	C20.1: Manufacture of basic chemicals, fertilisers and nitrogen compounds, plastics and synthetic rubber in primary forms
Analytical reagent	C20.59 Manufacture of other chemical products n.e.c.
Catalysts	C20.59 Manufacture of other chemical products n.e.c.
Chemical synthesis	C20: Manufacture of chemicals and chemical products
Coatings (formulation of paints and coatings)	C20.3: Manufacture of paints, varnishes and similar coatings, printing inks and mastics
Construction (wood preservation, flame retardants, formulation of borates in plaster board)	C20.3: Manufacture of paints, varnishes and similar coatings, printing inks and mastics Also in C23
Detergents	C20.4: Manufacture of soaps and detergents, cleaning and polishing preparations, perfumes and toilet preparations
Industrial fluids	C20.3 Manufacture of paints, varnishes and similar coatings, printing inks and mastics
Printing paper (PVA solutions)	C20.5 Manufacture of other chemical products n.e.c.
C23 Glass and ceramics	
Abrasives	C23.9 Manufacture of abrasive products and non-metallic mineral products n.e.c.
Cellulose insulation	C23.6 Manufacture of fibre cement C23.9 Manufacture of other non-metallic mineral products n.e.c.
Ceramics (production of frits)	C23.3 Manufacture of clay building materials C23.4 Manufacture of other porcelain and ceramic products
Construction (wood preservation, flame retardants, formulation of borates in plaster board)	C23.6 Manufacture of articles of concrete, cement and plaster Also in C20
Glass (production of glass wool, high alkali glass and low alkali glass)	C23 Manufacture of glass and glass products
Non-oxide Ceramics	C23.3 Manufacture of clay building materials C23.4 Manufacture of other porcelain and ceramic products
Refractories	C23.2 Manufacture of refractory products
Manufacturing sub group	
Food products	C10 Manufacture of food products
Pharmaceutical products	C21 Manufacture of basic pharmaceutical products and pharmaceutical preparations
Basic metals	C24 Manufacture of basic metals
Fabricated metal products	C25 Manufacture of fabricated metal products, except machinery and equipment
Computers	C26 Manufacture of computer, electronic and optical products
Motor vehicles	C29 Manufacture of motor vehicles, trailers and semi-trailers
Sources: RPA research	

X12.3.4 Use of specific borates by sector

The two commonest boron compounds are boric acid and disodium tetraborate, both are registered for 100,000 – 1,000,000 tonnes a year by REACH.

However, the exposure data and dose response relationships (DRRs) are only available converted to boron and not for each borate compound. Therefore, the number of exposed workers and cases of ill health has been calculated for one compound: boric acid. Boric acid is chosen because it is the most widely used as can be seen in Table X12-13 from a consultation of EBA members in 2018. This data is only available for the sectors supplied by EBA members. The assumption made is that all workers that are exposed to borates are exposed to boric acid for both subgroups, the chemicals and glass, and manufacturers.

Table X12-13: Borate reprotoxins - percentages of enterprises using a given compound by sector				
Category (see Table above)	**Diboron trioxode**	**Disodium tetraborate**	**Boric acid**	**Disodium octaborate**
C20 Chemicals	4%	46%	83%	12%
C23 Glass and ceramics	8%	61%	76%	12%
Other	6%	42%	88%	1%
All sectors	6%	47%	82%	8%
Source: European Borates Association *Notes*				

X12.4 Exposed workforce

No estimates of the number of workers exposed (or potentially exposed) to boron compounds in the EU have been identified from published literature.

The exposed workforce of the two sub groups being considered are the product of the percentage of the enterprises using borates, the percentage of exposed workers in a plant using borates, and the total number of workers in the sector. Some chemicals, 100% of borosilicate glass and 50% of manufacturing enterprises are believed to be using borates, therefore 50% of all enterprises in these sectors are assumed to be using borates. The percentage of exposed workers in any plant using borates is expected to be low and the percentage used for modelling taken as 10%.

X12.4.1 Total number of estimated exposed workers

The total number of workers in each sector is given in Table X12-14, together with the estimated number of 'potentially exposed' workers based upon 5% of all workers being exposed to boron. These figures for employee numbers are taken from the Eurostat data on employment by sex, age and detailed economic activity, and are used as the basis for the analysis, except analysis by Member State, see section X12.4.2

Table X12-14: Borate reprotoxins – estimated exposed workforce by sector (2015)		
Sector	**No of workers**	**Estimated no of exposed workers**
Chemicals and glass		
C20 Manufacture of chemicals and chemical products	1,296,100	64,805
C23 Manufacture of other non-metallic mineral products (glass and ceramics)	1,273,900	63,695
Total chemicals and glass	**2,570,000**	**128,500**

Table X12-14: Borate reprotoxins – estimated exposed workforce by sector (2015)		
Sector	**No of workers**	**Estimated no of exposed workers**
Manufacturing		
C10 Manufacture of food products	4,553,400	227,670
C21 Manufacture of basic pharmaceutical products and pharmaceutical preparations	832,600	41,630
C24 Manufacture of basic metals	1,151,900	57,595
C25 Manufacture of fabricated metal products, except machinery and equipment	3,588,400	179,420
C26 Manufacture of computer, electronic and optical products	1,528,700	76,435
C27 Manufacture of electrical equipment	1,346,800	67,340
C28 Manufacture of machinery and equipment n.e.c.	3,400,800	170,040
C29 Manufacture of motor vehicles, trailers and semi-trailers	3,241,300	162,065
C30 Manufacture of other transport equipment	1,000,100	50,005
D35.1 Electric power generation, transmission and distribution	1,140,990	57,050
E38.1 Waste collection	203,380	10,169
M72 Scientific research and development	925,300	46,265
Total manufacturing	**22,913,670**	**1,145,684**
Source: Eurostat (Employment by sex, age and detailed economic activity) and RPA analysis		

X12.4.2 Breakdown by Member State

A breakdown of employees in each sector by Member State is given in Table X12-15.

Table X12-15 provides the percentage of employees in each sector that are in a Member State that does not have an OEL for boric acid. Member States that have an OEL for boric acid for the dose response relationship are assumed to be operating beneath this OEL. Member States without an OEL are assumed to be operating at ten times the DNEL for the top 5 percentile of all exposed employees, see section X12.5.2.

Table X12-15: Borate reprotoxins – percentage of workers in Member States without an OEL		
Sector	**% of workers in Member States without an OEL**	**Estimated workers in Member States without an OEL**
Chemicals and glass		
C20 Manufacture of chemicals and chemical products	18%	11,665
C23 Manufacture of other non-metallic mineral products (glass and ceramics)	31%	19,745
Total	**-**	**31,410**
Manufacturing		
C10 Manufacture of food products	29%	66,024
C21 Manufacture of basic pharmaceutical products	24%	9,991

Table X12-15: Borate reprotoxins – percentage of workers in Member States without an OEL		
Sector	**% of workers in Member States without an OEL**	**Estimated workers in Member States without an OEL**
and pharmaceutical preparations		
C24 Manufacture of basic metals	26%	14,975
C25 Manufacture of fabricated metal products, except machinery and equipment	26%	46,649
C26 Manufacture of computer, electronic and optical products	22%	16,816
C27 Manufacture of electrical equipment	29%	19,529
C28 Manufacture of machinery and equipment n.e.c.	19%	32,308
C29 Manufacture of motor vehicles, trailers and semi-trailers	30%	48,620
C30 Manufacture of other transport equipment	18%	9,001
D35.1 Electric power generation, transmission and distribution	30%	17,115
E38.1 Waste collection	28%	2,847
M72 Scientific research and development	15%	6,940
Total manufacturing		**290,815**
TOTAL	**Average 31%**	**Total 322,225**
Source: Eurostat and RPA analysis		

Table X12-16: Borate reprotoxins – total workforce by Member State by sector														
Member State	Chemicals and glass		Manufacturing											
	C20	C23	C10	C21	C24	C25	C26	C27	C28	C29	C30	D35.1	E38.1	M72
Austria	17,285	30,355	71,857	23,880	35,720	72,219	21,225	45,245	79,787	31,141	7,006	24,150	9,900	12,600
Belgium	43,761	26,227	77,848	8,367	24,625	48,563	10,229	14,696	29,677	29,221		19,207	4,348	16,300
Bulgaria	13,643	20,882	78,664	9,110	11,682	54,562	9,357	21,362	30,895	20,950	4,851	26,547	9,553	9,300
Cyprus	606	1,738	10,625	32,529	286	2,712			485	114	28	2,130	380	
Czech Republic	28,136	53,323	90,652	128,356	44,182	149,990	40,536	90,820	121,995	156,864	22,481	16,455	20,770	23,000
Germany	330,991	229,268	754,218	314	264,113	841,703	334,922	481,291	1,103,354	849,075	132,050	198,672	67,793	220,200
Denmark	16,090	16,265	53,998		5,847	39,005	19,924	13,539	67,682	4,738	2,823	9,448	4,319	10,500
Estonia	2,519	4,372	13,759	9,030	525	12,810	5,784	5,447	3,901	3,288	682	3,038	1,172	2,000
Greece	10,189	12,132	83,592	39,009	8,049	18,437	2,481	5,844	7,869	1,411	3,037	21,329	2,151	6,700
Spain	82,006	81,022	300,534		57,058	202,980	23,541	61,254	96,981	142,425	44,414	30,895	69,923	62,800
Finland	12,857	13,852	35,463	4,847	14,580	38,681	24,280	17,475	47,974	7,124	7,857	11,595	2,158	28,600
France	147,935	109,294	488,785	57,387	76,211	308,413	131,757	109,014	178,534	223,114	152,800	140,409	41,068	173,200
Croatia	5,938	11,108	52,478	1,487	4,297	29,838	5,463	10,555	11,150	2,775	8,007	12,149	9,592	6,300
Hungary	14,760	23,813	91,074	2,039	17,238	73,243	43,970	39,892	60,788	88,392	5,287	13,981	9,101	13,400
Ireland		7,461	44,597	659	2,642	12,611		3,844		2,911	222		2,794	8,700
Italy	101,408	134,760	312,026		113,581	414,112	91,396	140,691	424,114	157,960	79,085	60,006	90,691	62,300
Lithuania	5,419	8,077	39,503	17,432	633	13,984	3,351	4,829	6,245	4,407	1,892	5,757	3,319	
Luxembourg	1,008	2,261	5,085	1,165		3,619		489	4,012				632	1,100
Latvia	2,728	5,271	21,184	12,722	1,294	10,358	1,789	2,652	3,611	1,830	2,068	5,765	3,065	2,200
Malta	278	1,238		14,121		1,111		514						
Netherlands	43,633	19,871	117,235	22,722	19,430	82,521	25,803	19,634	79,780	19,915	17,359		10,122	37,700
Poland	76,026	120,160	373,783	6,247	61,055	269,921	57,135	100,943	120,602	176,986	42,460	72,604	37,707	33,700
Portugal	11,833	37,344	87,933	9,249	7,628	75,021	9,000	18,532	21,741	33,123	4,306	7,841	5,681	7,900
Romania	24,044	38,614	160,363		29,910	89,498	31,672	40,051	51,605	168,588	30,738	51,596	31,258	9,800
Sweden	18,520	17,566	49,547	2,217	32,349	65,539	15,498	22,435	68,443	66,099	18,421	20,135	9,017	35,100
Slovenia	6,297	6,868	13,407		8,307	28,986		20,000	13,401	12,706	608	6,589	3,071	5,200
Slovakia	8,494	14,392	32,790	11,891	22,197	49,944	14,175	31,301	40,228	66,324	4,109	10,339	4,332	6,500
United Kingdom	101,523	80,155	371,981		66,746	328,591	112,059	88,123	191,793	152,512	139,358	94,677	51,783	126,100
Total (1)	**1,127,927**	**1,127,689**	**3,832,981**	**414,780**	**930,185**	**3,338,972**	**1,035,347**	**1,410,472**	**2,866,647**	**2,423,993**	**731,949**	**865,314**	**505,700**	**921,200**

Source Eurostat and RPA analysis

Notes 1 Totals taken from Eurostat data for employees by Member State are lower than those from the Eurostat data for employees by age and sex used in all other calculations

X12.4.3 Breakdown by gender and age

Borates have different reproductive effects upon exposed male and female workers. Therefore, to calculate the number of cases of ill health, the percentage of employees in each sector who are of reproductive age and sex is given in Table X12-17. Women between 15 and 49, and all men, are taken as being of reproductive age.

Table X12-17: Borate reprotoxins – percentages of exposed workforce of reproductive age by sex and sector.

Sector	% of exposed workers Male >15	% of exposed workers Female 15-49	% of exposed workers of reproductive age
Chemicals and glass			
C20 Manufacture of chemicals and chemical products	69%	23%	92%
C23 Manufacture of other non-metallic mineral products (glass and ceramics)	78%	15%	93%
Manufacturing			
C10 Manufacture of food products	56%	32%	88%
C21 Manufacture of basic pharmaceutical products and pharmaceutical preparations	53%	36%	89%
C24 Manufacture of basic metals	86%	10%	96%
C25 Manufacture of fabricated metal products, except machinery and equipment	84%	11%	95%
C26 Manufacture of computer, electronic and optical products	67%	24%	91%
C27 Manufacture of electrical equipment	68%	23%	92%
C28 Manufacture of machinery and equipment n.e.c.	82%	12%	95%
C29 Manufacture of motor vehicles, trailers and semi-trailers	76%	19%	95%
C30 Manufacture of other transport equipment	84%	12%	96%
D35.1 Electric power generation, transmission and distribution	76%	18%	94%
E38.1 Waste collection	82%	13%	95%
M72 Scientific research and development	54%	36%	90%
Sources: Eurostat and RPA analysis			

X12.4.4 Births to workers each year

Several of the potential reprotoxic effects of borates affect the children of exposed workers. Based upon the Eurostat crude birth rates for men/women, 2.83% of female workers of reproductive age has a baby each year and 1% of male workers' partners have a baby each year.

X12.4.5 Trends

Table X12-18 shows the total percentage change in workforce between 2009 and 2017 by sector. In the chemicals sector C20, the total number of employees has varied little over the period 2009 to 2017. However, the workforce is ageing and the number of employees over 50 has increased by 14% and the number of employees aged 15-49 has decreased by 6%. There is a difference in the change between the sexes: the number of male workers over 50 has increased by 11% and the number of male workers aged 15-49 has decreased by 6%. Although all male workers are taken as being of reproductive age, fewer men tend to have children after 50 and therefore the increasing percentages of male workers over 50 is still relevant. Female workers over 50 have increased in number by 43% whereas female workers aged 15-49 have decreased in number by 10%.

In the glass sector C23, there has been an overall decrease of 12% in the total number of employees over the period 2009 to 2017. Again, the workforce is ageing: even though the overall workforce is decreasing, the number of men over 50 has increased in number by 14% and women over 50 by 44%.

In the manufacturing sub group, all but two sectors have relatively steady numbers of employees, with changes of between -4% and 6%. The exceptions are C24 (manufacturing of base metals) and D35.1 (electric power transmission), which declined in workforce by 12% and 7% respectively between 2009 to 2017

Three further sectors have growing workforces C28 (manufacture of machinery), C29 (manufacturing of vehicles etc) and E38.1 (waste collection) whose number of employees grew by 11, 20 and 17% respectively. However, the growth in numbers of women of reproductive age in two sectors, C28 and D38.1, are approximately zero, whilst the number of women in C29 grew by 24%.

Nonetheless, all of these industries also have ageing workforces, with all except C24 (manufacturing of base metals) having increases in both male and female workforces over 50. The rise in female workforce over 50 is over 20% in every sector except C24 (base metals) and C27 (manufacture of electrical equipment).

Table X12-18: Borate reprotoxins – percentage change in workforce between 2009 and 2017 by sector									
Sector	**All employees**	**Employees >50**	**Employees 15-49**	**Male employees >50**	**Male employees 15-49**	**Male employees >15**	**Female employees >50**	**Female employees 15-49**	**All emp of repro age, M >15 & F 15-49**
Chemicals and glass									
C20 Manufacture of chemicals and chemical products	-2%	14%	-8%	11%	-8%	-3%	43%	-10%	-5%
C23 Manufacture of other non-metallic mineral products (glass and ceramics)	-12%	16%	-22%	14%	-23%	-13%	44%	-15%	-14%
Manufacturing									
C10 Manufacture of food products	4%	33%	-4%	27%	-4%	3%	42%	-5%	0%
C21 Manufacture of basic pharmaceutical products and pharmaceutical preparations	6%	37%	-1%	37%	6%	12%	37%	-7%	4%
C24 Manufacture of basic metals	-12%	4%	-18%	4%	-19%	-12%	-6%	-11%	-12%
C25 Manufacture of fabricated metal products, except machinery and equipment	-4%	22%	-13%	22%	-12%	-3%	32%	-21%	-6%
C26 Manufacture of computer, electronic and optical products	-1%	34%	-11%	31%	-11%	-2%	37%	-9%	-4%
C27 Manufacture of electrical equipment	-2%	10%	-5%	11%	-1%	2%	6%	-13%	-2%
C28 Manufacture of machinery and equipment n.e.c.	11%	33%	3%	32%	3%	11%	54%	2%	9%
C29 Manufacture of motor vehicles, trailers and semi-trailers	20%	40%	15%	35%	12%	17%	68%	24%	19%
C30 Manufacture of other transport equipment	4%	21%	-2%	15%	-2%	2%	75%	5%	3%
D35 Electric power generation, transmission and distribution (1)	-6%	11%	-12%	9%	-14%	-7%	35%	-8%	-7%
E38 Waste collection (1)	17%	58%	2%	62%	2%	18%	216%	0%	15%
M72 Scientific research and development	10%	17%	8%	5%	9%	8%	47%	4%	6%

Sources: Eurostat and RPA analysis

Notes: 1 Data for D35.1 and E38.1 are unavailable and data for D35 and E38 are used instead. Trends in age and sex are likely to be similar in the sub sector to those in the whole sector.

X12.4.6 Exposed workers: conclusion

Table X12-19 shows the estimated exposed workforce based upon a given percentage of the workforce in plant using boron, in Member States without an OEL and being of reproductive age, by sector. The annual rate of change taken forward for modelling assumes that the rate of increase or decrease over the period 2009 to 2017, as shown in Table X12-18, is continued into the future.

Table X12-19: Borate reprotoxins – estimated exposed workforce and annual rate of change based upon a given percentage of the workforce in plant using boron, in Member States without an OEL and being of reproductive age by sector			
Sector	**Exposed workers of reproductive age**	**Male exposed workers of reproductive age, over 15**	**Female exposed workers reproductive age, 15-49**
Chemicals and glass sub group			
C20 Manufacture of chemicals and chemical products (100%)			
Estimated number of workers taken forward for modelling (10%)	10,995	8,272	2,723
Annual rate of change	-0.6%	-0.4%	-1.2%
C23 Manufacture of other non-metallic mineral products (glass and ceramics) (100%)			
Estimate taken forward for modelling (10%)	18,298	15,377	2,921
Annual rate of change	-1.7%	-1.5%	-1.8%
Chemicals & glass total	**29,294**	**23,649**	**5,645**
Manufacturing sub group			
C10 Manufacture of food products (50%)			
Estimate taken forward for modelling (10%)	58,354	37,213	21,140
Annual rate of change	0	0.4%	-0.6%
C21 Manufacture of basic pharmaceutical products and pharmaceutical preparations (50%)			
Estimate taken forward for modelling (10%)	8,915	5,290	3,625
Annual rate of change	0.5%	1.4%	-0.8%
C24 Manufacture of basic metals (50%)			
Estimate taken forward for modelling (10%)	14,598	13,076	1,523
Annual rate of change	-1.4%	-1.4%	-1.3%
C25 Manufacture of fabricated metal products, except machinery and equipment (50%)			
Estimate taken forward for modelling (10%)	44,099	39,137	4,962
Annual rate of change taken forward for modelling	-0.7%	-0.4%	-2.4%
C26 Manufacture of computer, electronic and optical products (50%)			
Estimate taken forward for modelling (10%)	15,616	11,435	4,181
Annual rate of change	-0.5%	-0.2%	-1.1%
C27 (50%) Manufacture of electrical equipment			
Estimate taken forward for modelling (10%)	18,172	13,556	4,617
Annual rate of change	-0.2%	0.2%	-1.5%
C28 (50%) Manufacture of machinery and equipment n.e.c.			
Estimate taken forward for modelling (10%)	30,531	26,524	4,008

Table X12-19: Borate reprotoxins – estimated exposed workforce and annual rate of change based upon a given percentage of the workforce in plant using boron, in Member States without an OEL and being of reproductive age by sector			
Sector	**Exposed workers of reproductive age**	**Male exposed workers of reproductive age, over 15**	**Female exposed workers reproductive age, 15-49**
Annual rate of change	1.1%	1.3%	0.2%
C29 Manufacture of motor vehicles, trailers and semi-trailers (50%)			
Estimate taken forward for modelling (10%)	46,577	37,168	9,409
Annual rate of change	2.2%	2.0%	2.7%
C30 (50%) Manufacture of other transport equipment			
Estimate taken forward for modelling (10%)	8,529	7,452	1,077
Annual rate of change	0.4%	0.2%	0.6%
D35.1 (50%) Electric power generation, transmission and distribution			
Estimate taken forward for modelling (10%)	16,126	13,102	3,024
Annual rate of change	-0.8%	-0.8%	-1.0%
E38.1 (50%) Waste collection			
Estimate taken forward for modelling (10%)	2,722	2,353	369
Annual rate of change	1.8%	2.1%	0%
M72 (50%) Scientific research and development			
Estimate taken forward for modelling (10%)	6,182	3,710	2,472
Annual rate of change	0.7%	1.0%	0.5%
Total manufacturing	**270,421**	**210,016**	**60,407**
Total all sectors	**299,715**	**233,665**	**66,052**
Source: Eurostat (2015) and RPA research			

X12.5 Exposure levels

X12.5.1 Exposure routes

Boron exposure occurs to boron compounds that are basically variants on boric acid. All of them metabolize (actually convert) to boric acid under standard physiological conditions. Given that dust generated during borate compound handling is the main exposure route, inhalation is the prevalent route into the human body. Oral and dermal exposure is much less important routes especially given that boric acid (and its analogues) are not absorbed well into the skin. Dermal exposure can cause skin irritation and similar occupational exposure problems. In an occupational setting, oral exposure is less important but in areas with high background boron levels, non-occupational exposure via dietary and water sources can play an important role.

X12.5.2 Current exposure levels

The two main sources of exposure data found in the EU are the chemical safety reports (CSRs) and the IFA's MEGA database for measurements in several sectors in Germany. These are shown in Table X12-20 and X12-21. Several studies report the exposure levels in environments where the exposure levels are known to be high and these are shown in Table X12-22. None of these studies report any ill-health effects as a result of these exposure levels. Table X12-22 also contains with the exposure levels at a

routine monitoring inspection provided by a respondent to the consultation. Other comments from the consultation included:

- Large pharmaceutical company: "*All air measurement outcomes are either less than 10% of the TLV, or below the Detection Limit*"
- Large manufacturing company: boric acid – exposure readings below detection limit
- Large user: "*Typically dust and B are measured. Results are expressed in mg/m^3 air. Values are always within the relevant regulatory limits, based on national legislations.*"
- Large chemicals company: "*All the results are below the occupational exposure limits.*"
- Large user: Exposure limit for boron has an average of 0.29 mg/m^3"

From the tables, the exposure levels for 95% of the exposed workforce can be estimated for several sectors. In all cases, the level for the 95th percentile is much lower than the lowest threshold for ill-health effects shown above. From the CSRs, there are two exposure scenarios that apply to the chemicals and glass industries and many of the manufacturers, which have recorded exposure levels that are above the lowest threshold for ill-health effects. However, the 90th percentiles values for both of these scenarios are below this threshold.

Taking all of the information into account, the study team assumes that only the top five percentile of workers are exposed to concentrations above the lowest threshold for ill-health effects. For this study, the exposure level experienced by this group of workers is taken to be ten times the DNEL for boric acid. Table X12-23 shows the DNELs for all borate compounds converted to their boron equivalent. The DNEL for boric acid is 1.45mg/m^3 and therefore the exposure level representing the top five percentile of exposed workers for analysis is 14.5mg/m^3. This is higher than any exposure levels measured in the CSRs.

Figure X12-2 shows all of the key exposure level measurements found, the DNELs and OELs for the various borate compounds converted to boron equivalent, the proposed exposure level (14.6mg/m^3) for the top 5 percentile of exposed workers, and the two dose response relationships for endpoints with thresholds below this level.

Table X12-20: Borate reprotoxins – approximate exposure levels for CSR exposure scenarios

Exposure scenario	Approximate range (mgB/m^3)	90th percentile below threshold
ES8 - Discharging big bags (750-1500kg) into mixing vessels	0 - 10	Y
ES15 - Off-loading borates from ships	0 - 10	N
ES20 - Packaging into big bags (750-1500kg)	0 - 10	N
ES21 - General maintenance activities	0 - 10	Y
Remaining 37 exposure scenarios	0 – DNEL	Y, below DNEL
Source: Chemical safety reports for borates		

Table X12-21: Borate reprotoxins – exposure concentrations (1)of boron and its compounds

Sector and associated NACE sector Activities	Number of measured data	Number of firms	Concentration in mg/m^3		
			50 percentile (5)	90 percentile (5)	95 percentile (5)
Chemicals and glass sub group					
Chemical industry (C20)	11	6	0.008 (2)	0.125 (2)	0.226 (2)
Flat glass, hollow glass (C23)	32	6	0.0012 (2)	0.017	0.023

Table X12-21: Borate reprotoxins – exposure concentrations (1)of boron and its compounds					
Sector and associated NACE sector Activities	Number of measured data	Number of firms	Concentration in mg/m³		
			50 percentile (5)	90 percentile (5)	95 percentile (5)
Stones and earths, fine mechanics, glass industry (C23)	21	7	0.002 (2)	0.061 (2)	0.155 (4)
Manufacturing sub group					
Electrical engineering (C27)	22	18	- (4)	0.018 (2)	0.021 (2)
Electroplating (C16)	48	27	- (4)	0.01 (2)	0.022 (2)
Treatment of wood (C20)	17	7	0.001 (2)	0.028 (2)	0.05 (2)
Processing and treatment of metals (C25)	47	23	0.003 (2)	0.031 (2)	0.05 (2)
Manufacture of machinery an vehicles (C28, C29 and C30)	15	8	0.002 (2)	0.015 (2)	0.015 (2)
Other sub groups					
Construction (F)	12	3	0.002	0.015	0.07

Source: IFA MEGA evaluations: Boron and its compounds (2012)
https://www.dguv.de/medien/ifa/en/fac/reach/mega_auswertungen/boron.pdf
Notes 1 Air concentrations were measured for between one and six hours
2 The distribution value is not below the largest analytical quantification limit in the data set
3 The limit of quantification is 0.002mg/m³
4 The number of measured values below the analytical quantification limit is greater that the number of measured values represented by this cumulative frequency value. No concentration is therefore given for this cumulative frequency value.
5 If any single values fell below the measurement method's analytical quantification limit, half of each value was adopted in this evaluation.

Table X12-22: Borate reprotoxins – exposure concentrations of boron and its compounds			
Sector	Exposure scenario	Number of employees	Total amount inhaled BORON (mg/m³)
Chemicals	Boric acid production plant in Turkey (1)	Control N=102 Exposed N=102	Control 0.47 Exposed 0.74 – 1.45 Low - high
Chemicals	Highly exposed workers in a boric acid production plant in Turkey (2)	N=204	0.12 High
Chemicals	Extreme exposure conditions in a boric acid production plant in Turkey (3)	Unknown	0.04 – 0.12 Low - high
Chemicals	Workers were exposed occupationally to sodium borates in USA (4)	N=336	2.09 High
Anonymous	Workplace monitoring of a plant that bulk handles borates in EU (5)	Under 50	Below threshold

Table X12-23: Borate reprotoxins – DNELs, boron equivalents and converted DNELs			
Name & CAS number	**DNEL mg/m³**	**Boron equivalent**	**Converted DNEL mg/m³**
Diboron trioxide 1303-86-2	4.66	3.2	1.47
Disodium tetraborate, anhydrous 1330-43-4 1303-96-4 12179-04-3	6.7	 8.8 4.7 6.7	1.43
Boric acid 10043-35-3	8.3	5.7	1.45
Perboric acid, sodium salt 10332-33-9 11138-47-9 12040-72-1	2		
Disodium octaborate 12008-41-2, 12280-03-4	6.9	14.28	0.48
Source: ECHA registration dossiers, RPA analysis			

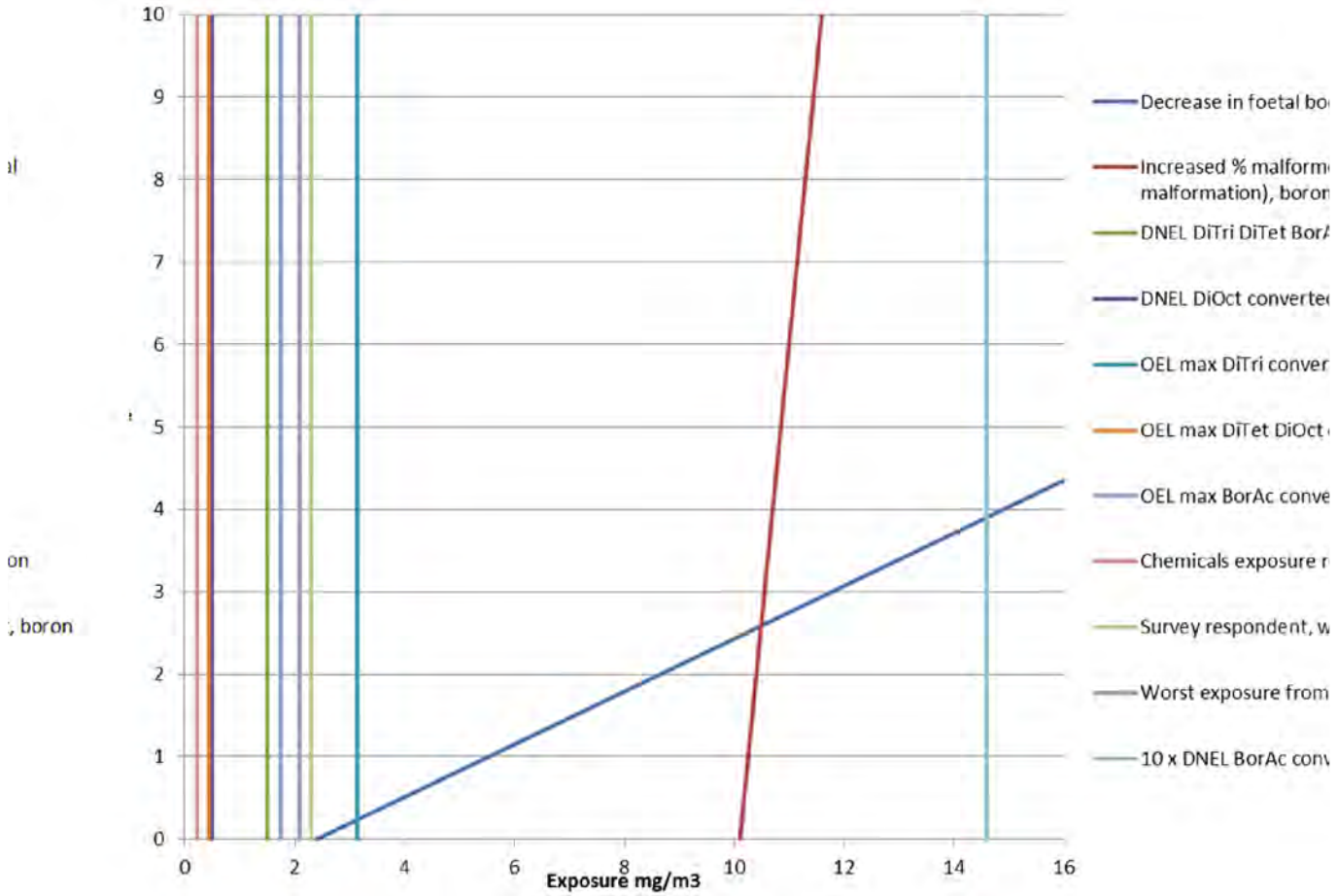


Figure X12-2: Borate reprotoxins – two dose response relationships with the lowest thresholds compared with OELs, DNELs and specific exposure levels measured.
Source: RPA analysis
Notes: OELs and DNELs for boron compounds converted to boron equivalents

X12.5.3 Trends

The consultation responses give some insight into the likely future exposure trends and indicate an expectation that exposure levels will continue to decrease:

- Large chemicals company: "*The restriction in EU on no longer being able to sell pesticides that are labelled Cat 1 CMR coming into play in 2021, there will be a need to remove any Cat1 CMR components in the formulated products. Thus, the requirements for handling should decrease.*"
- Large chemicals company: "*Our company has a policy to substitute and/or reduce the exposure to reprotoxicants 1A/1B based on the identification of CMR substances (inventories), on the search of safer alternatives (elimination, substitution, change of the physical state) and on a specific risk management. All risk management measures must be technically and economically feasible*."
- Large user: "*Comparing to previous dust monitoring results, we have already seen improvements in the most recent one. We believe that it will be further reduced*."

X12.6 Current Risk Management Measures (RMMs)

X12.6.1 Overview of RMMs

Based upon the consultation, 10 of the 12 companies replying to the question about activities to prevent and reduce exposure (collective measures such as closed systems and ventilation) say that this was "complete for some or all substances" and two said "yes, in progress, but not yet complete". Examples of closed systems and ventilation measures used that were noted in the open ended question included:

- *"[Air] conditioning of relevant production lines, dust collectors and ventilation, air conditioning in front end loaders"*
- *"Personal protective equipment is used, laboratory areas are designed so that risk is minimal (sufficient air exchange per hour...)*
- *"closed systems, isolators, glove boxes, fume hoods, ventilation"*
- *"The products are produced and promoted in closed systems where possible. Contact with the substances is given when these systems are opened for maintenance, servicing, quality control or bottling. Exhausts are installed in places where natural ventilation is not sufficient or extraction measures are required"*
- *"Use of closed systems and use of ventilation are examples of collective measures which have been used."*

X12.6.2 REACH measures

Risk management measures for the borate substances as recommended from REACH registration information are summarised in Table X12-24.

Borate substances have been registered under REACH for a wide variety of uses and all PROC codes 1-26 are relevant for boric acid. PROC codes where exposure could occur for boric acid include:

- PROC 4 (Chemical production where opportunity for exposure arises);
- PROC 7 (Industrial spraying);
- PROC 10 (Roller application or brushing);

- PROC 15 (Use as a laboratory reagent); and
- PROC 26 (Handling of solid inorganic substances at ambient temperature)

For the borate substances, the recommended risk management measures are similar for each borate substance. Respiratory protection is recommended with dust proof goggles also listed (for eye protection). Protective clothing is also recommended with showers and eye wash stations are also required.

Table X12-24: Borate reprotoxins – Recommended RMMs for borates from REACH registrations

Substance	Measure	Details
Diboron trioxide	Organisational measures	Ensure adequate ventilation; LEV for ensuring airborne concentrations are below permissible exposure limits
	Respiratory protection	Respirators should be used (CEN 149) where the airborne concentrations are expected to exceed the exposure limit
	Skin and body protection	Wear gloves (rubber, nitrile, butyl) if dusty
Disodium tetraborate, anhydrous	Organisational measures	Ensure adequate ventilation; LEV for ensuring airborne concentrations are below permissible exposure limits
	Respiratory protection	Respirators should be used (CEN 149) where the airborne concentrations are expected to exceed the exposure limit
	Skin and body protection	Eye protection is required (CEN149); Wear gloves (rubber, nitrile, butyl) if dusty
Boric acid	Organisational measures	Ensure adequate ventilation; LEV for ensuring airborne concentrations are below permissible exposure limits
	Respiratory protection	Respirators should be used (CEN 149) where the airborne concentrations are expected to exceed the exposure limit
	Skin and body protection	Wear gloves (rubber, nitrile, butyl) if dusty
Perboric acid, sodium salt	Organisational measures	Adequate ventilation
	Respiratory protection	Wear respirator with dust filter
	Eye protection	Dust proof goggles
	Skin and body protection	Protective clothing and shoes; rubber gloves
	Other	Showers and eye wash stations
Disodium octaborane	Organisational measures	Ensure adequate ventilation; LEV for ensuring airborne concentrations are below permissible exposure limits
	Respiratory protection	Respirators should be used (CEN 149) where the airborne concentrations are expected to exceed the exposure limit
	Skin and body protection	Wear gloves (rubber, nitrile, butyl) if dusty

Sources: ECHA (2018): Boric acid REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15472/9
ECHA (2018): Disodium tetraborate, anhydrous REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15357/9
ECHA (2018): Diboron trioxide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15317/9
ECHA (2018): Perboric acid, sodium salt REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/13523/9
ECHA (2018): Disodium octaborane REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14136/9

X12.6.3 Safety data sheets

Measures for reducing exposure to boric acid are also provided by suppliers to their downstream users through Safety Data Sheets (SDS). These list control parameters (components with workplace control parameters), appropriate engineering controls, eye/face protection, skin protection, body protection and respiratory protection recommended for handling the substance.

The recommended exposure controls are similar to those recommended in the Registration dossier with some additional measures recommended. For example, for boric acid, the additional measures listed are:[479]

- Eye protection (Safety glasses with side shields- EN166) is recommended;
- Impervious clothing is recommended for body protection;
- Respiratory protection recommended is to use a full face particle respirator type P3 (EN 143) respiratory cartridges as a backup to engineering controls; and
- Where there are no controls, a full-face supplied air respirator is recommended.

Interestingly, the safety data sheet for disodium tetraborate, anhydrous states that technical measures and appropriate working operations should be prioritised over the use of PPE and to use respiratory protection where dusts are generated.

X12.6.4 Consultation responses

The risk management measures implemented by companies to reduce workplace exposure to borates are discussed in the following tables. The processes for which the substances are used and the exposure concentrations experienced are discussed illustrating the effect of risk management measures on workplace exposure. Generally, risk management measures for borates:

- Involves the use of PPE for workers;
- Involves the use of closed systems and other measures if necessary;
- Separation of work and personal clothing;
- Involves hygiene measures, such as no eating and drinking; and
- Exposure duration varies from a couple of minutes to a full work shift.

The number of measurements of exposure concentration reported from the consultation is limited, and concentrations range from <LOD to 0.72 mg/m^3 and describe the RMMs in place for these measurements.

Table X12-25: Borate reprotoxins – RMMs used for the handling of borates by companies

Substance	Operation	RMMs used	Other practices	Exposure (duration, concentration)
Borates	Electroplating; metallisation; soldering; production line operators; maintenance workers	Restricted areas; PPE classified by the work place and EN standard	No eating, drinking and smoking at the work site; separate storage	7.5 hours a day for production operators; 1 hour a day for

[479] Sigma Aldrich (2017): Boric acid Safety Data Sheet. Available at: https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=185094&brand=ALDRICH&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2F185094%3Flang%3Den

Table X12-25: Borate reprotoxins – RMMs used for the handling of borates by companies				
Substance	**Operation**	**RMMs used**	**Other practices**	**Exposure (duration, concentration)**
			of work and personal clothing; workers complete chemicals safe handling course	maintenance workers H_3BO_3 exposure level is below the detection level
Boric acid	Manufacturing of fertilisers	PPE; standard operating procedures; SDS; Labelling	-	-
Boric acid; disodium tetraborate anhydrous; disodium octaborane	Manufacture of other basic inorganic compounds	P2 or P3 face masks (compulsory for some operations);	No eating, drinking and smoking on site; separate storage of work and personal clothing; SDS are used; on site washing facilities	6-7.5 hours per day for 5 days a week
Diboron trioxide; disodium tetraborate, anhydrous	Manufacture of other inorganic basic chemicals Mining of chemical and fertiliser minerals • Warehousing and storage • • Loading/unloading, milling, packaging, maintenance	P2 or P3 PPE used (compulsory for some activities);	No eating, drinking and smoking on site; separate storage for work and personal clothing; on site washing facilities; periodic training on risks; SDSs are used	-
Disodium tetraborate, anhydrous	Manufacture of pharmaceuticals (laboratory)	Closed systems; glove boxes, fume hoods and ventilation used; restricted areas for authorised workers only; PPE: depends on risk assessment, but safety gloves, respiratory protection, safety glasses, safety shoes and protective clothing may be used	Hazard signs used; separate storage of personal and work clothing; training on risk management measures	5 mins per day and <10 times per year
Disodium tetraborate, anhydrous	Packing, discharging, loading/unloading	RMMs as specified in SDS; workers are trained on the use of PPEs		0.722 mg/m^3
Source: RPA Consultation with companies through questionnaires				

X12.6.5 Best/good practice examples

The consultation gave many examples of best practice for managing occupational risks to reproductive health following the hierarchy of preventive and protective measures in the CAD and CMD to comply with the requirements of the directives, and how they could be made available to stakeholders limiting an additional burden for them. These quotes from the consultation reflect the views of most respondents:

- Large chemicals company *"All materials are handled under strictly controlled conditions. We use either OELs or hazard categories to drive the required control approach, as mandated by regulations such as COSHH/REACH. Our aim is that no worker will be exposed."*
- Large chemicals company "*Pesticide production is usually via batch formulation, typically exposure would be less than 1 hour per shift. Batches times typically not more than 2 months. Most large scale production is heavily mechanised, 2-3 operators per shift, often working in a remote control room. Equipment and plant are cleaned before being worked on by maintenance staff."*
- Large pharmaceutical company *"Most of the above listed substances is used for laboratory tests and not routinely. Many of them are used for short periods, lasting one month as maximum. In laboratory tests the quantities used range from milligrams to grams, with a daily exposure duration of a few minutes. The frequency of exposure and the used quantities for Disodium tetraborate, anhydrous (CAS 1303-96-4): frequency less than 10 days/year; exposure duration 5 min/day; quantity less than 10."*

Two of the 14 companies using borates in the consultation indicated that they make use of the "slight risk" provision under the CAD, with one respondent, a large pharmaceutical company noting that *"this is relevant [..] to laboratory tests."* A respondent that does not use the "slight risk" provision, a large chemical company, adds "*for reprotoxic substances 1A/1B, we don't use the light (sic) risk"* provision.

Regarding question 13 about substitution, in the consultation, there were twelve responses about the replacement of the relevant substance(s) and they were:

- Yes complete - 1 reply
- Yes in progress - 2 replies
- Yes, considered but not feasible - 4 replies
- No, not considered - 5 replies, (all involved in the supply and wholesaling of borates)

One respondent added *"Disodium tetraborate, anhydrous (CAS 1303-96-4): substitution in progress but not completed yet Procedures are in place to ensure that the use is authorized only when there isn't any technically possibility to replace the substance."*

Question 15 asked whether the company carried out any activities to restrict access to risk areas, such as demarcate relevant areas and restrict access to authorised workers. Nine respondents of the twelve who replied said that this was "complete for some or all substances" and two said it was "considered, but not feasible" and one said it was "not considered". The activities noted in the open ended question included:

- *"Access to restricted area is restricted by risk assessment- these areas are locked."*
- *"Dangerous chemicals are under lock and key."*
- *"Restricted access to authorized workers controlled by badge, demarcation of the risks areas, hazard signs."*

- *"Areas with reprotoxicants 1A/1B are usually marked with pictograms and sometimes restricted access is put in place."*
- *"Product name reported on various areas; access to the warehouse and to the loading station closed and locked, only open by authorized workers; toll box in each area with safety information."*

Question 16 asked whether the company carried out any health surveillance/monitoring activities and of the twelve that replied, ten respondents of the twelve who replied said that this was "complete for some or all substances" and one said it was "in progress " and one said it was "considered, but not feasible". The activities noted in the open ended question included:

- *"Medical examination performed by workplace medicine institution."*
- *"Regular health exams for all employs."*
- *"Specific health surveillance and monitoring are performed periodically and before employment."*
- *"Dust monitoring [in place]"*

Question 17 asked whether the company carried out any activities with regard to planning for unforeseen/accidental exposure and of the twelve that replied, ten respondents of the twelve who replied said that this was "complete for some or all substances" and two said it was "considered, but not feasible".

Question 18 asked whether the company carried out any activities with regard to personal protection measures such as provision, specification, maintenance and storage of personal protective equipment (PPE) and all twelve that responded said that this was "complete for some or all substances". The personal protective equipment noted in the open ended question included:

- *"PPE, mainly masks (P2 or P3) are available in every relevant area. These are compulsory in some specific activities. They are always available and controlled for the proper category."*
- *"PPE is only considered as an appropriate secondary control. PPE is maintained and stored following internal requirements. This is also subject to Audit."*
- *"The provision, specification, maintenance and storage of personal protective equipment (PPE) are based on risk assessment outcomes: safety gloves, Respiratory Protective Equipment (RPE), safety glasses, safety shoes and protective clothing."*
- *"Even before the harmonised classification, all our workers were equipped with relevant PPEs such as: overalls, safety shoes, gloves, glasses, masks (i.e.P2/P3 respirators)."*

Question 19 asked whether the company carried out any activities about personal hygiene requirements such as no eating/smoking/drinking, separate storage of work and street clothes and washing/toilet facilities and all twelve that responded said that this was "complete for some or all substances".

Question 20 asked whether the company carried out any activities about the provision of information/training to workers and their participation in decision making and all twelve that responded said that this was "complete for some or all substances".

Question 21 asked whether the company carried out any activities with regard to record keeping and provision of information to the authorities and of the eleven that replied, ten respondents of the twelve who replied said that this was "complete for some or all substances".

X12.6.6 Protecting pregnant women, breastfeeding mothers and young people

In the consultation, question 22 asked about special measures that are relevant to reprotoxic substances such as the protection of pregnant women, breastfeeding mothers and young people, and ten of the fourteen respondents gave details about such as:

- Large user: *"Pregnant women, Breastfeeding mothers and underage people are not allowed in the plant."*
- Large manufacturer: *"They are instantly transferred to another workplace without possibility of being exposed to reprotoxic substances"*
- Large pharmaceutical company: *"Pregnant women, breastfeeding mothers are not working in laboratories during that stage of their life."*
- Large chemicals company: *"We recognise that some reproductive materials affect the male reproductive organs not female. Thus we design our control approaches to protect all workers, male, female and pregnant females, We also make provisions to allow pregnant and /or breastfeeding females to be redeployed during this period."*
- Large pharmaceutical company: *"Large pharmaceutical company: "Pregnant women, breastfeeding mothers are not working in laboratories during that stage of their life."*
- Large user: *"In warehouses, most of the workers are males. Therefore, women/pregnant women/breast-feeding women do not expose to reprotoxic substances."*

X12.6.7 Voluntary industry initiatives

Two voluntary industry initiatives to reduce exposure to borates were found:

- CEFIC product stewardship;
- Fertilisers Europe product stewardship.

X12.7 Market analysis

X12.7.1 Estimated numbers of enterprises with exposed workers

The total number of enterprises in each sector is given in Table X12-26, together with the estimated number of 'potentially exposed' enterprises based upon 50% of all enterprises in the chemicals and glass sub group using boron, and 50% of all enterprises in the manufacturing sub group using boron. These are the same percentages that were used to arrive at exposed workers in these sectors.

Table X12-26: Borate reprotoxins – estimated number of enterprises and estimated exposed enterprises split by size for 2015

Sector	No of enterprises	Estimated no of exposed enterprises	Percentage (size)
Chemicals and glass (50%)			
C20 Manufacture of chemicals and chemical products Total	29,556	14,778	100%
Micro	19,620	9,810	66%
Small	6,158	3,079	21%
Medium	2,954	1,477	10%
Large	825	413	3%

Table X12-26: Borate reprotoxins – estimated number of enterprises and estimated exposed enterprises split by size for 2015			
Sector	**No of enterprises**	**Estimated no of exposed enterprises**	**Percentage (size)**
C23 Manufacture of other non-metallic mineral products (glass and ceramics) Total	93,903	46,952	100%
Micro	85,826	42,913	91%
Small	4,400	2,200	5%
Medium	2,920	1,460	3%
Large	742	371	1%
Total - chemicals and glass	**123,459**	**76,508**	
Manufacturing (50%)			
C10 Manufacture of food products Total	265,853	132,927	100%
Micro	210,617	105,309	79%
Small	42,669	21,335	16%
Medium	10,164	5,082	4%
Large	2,401	1,201	1%
C21 Manufacture of basic pharmaceutical products and pharmaceutical preparations Total	4,181	2,091	100%
Micro	2,105	1,053	50%
Small	865	433	21%
Medium	737	369	18%
Large	469	235	11%
C24 Manufacture of basic metals Total	16,560	8,280	100%
Micro	10,378	5,189	63%
Small	3,613	1,807	22%
Medium	1,877	939	11%
Large	692	346	4%
C25 Manufacture of fabricated metal products, except machinery and equipment Total	384,404	192,202	100%
Micro	317,753	158,877	83%
Small	54,695	27,348	14%
Medium	10,675	5,338	3%
Large	1,280	640	0%
C26 Manufacture of computer, electronic and optical products Total	40,954	20,477	100%
Micro	30,727	15,364	75%
Small	7,012	3,506	17%
Medium	2,505	1,253	6%
Large	710	355	2%
C27 Manufacture of electrical equipment Total	46,760	23,380	100%
Micro	34,760	17,380	74%
Small	8,030	4,015	17%
Medium	3,040	1,520	7%
Large	940	470	2%
C28 Manufacture of machinery and equipment n.e.c.	90,028	45,014	

Table X12-26: Borate reprotoxins – estimated number of enterprises and estimated exposed enterprises split by size for 2015			
Sector	**No of enterprises**	**Estimated no of exposed enterprises**	**Percentage (size)**
Total			
Micro	57,382	28,691	64%
Small	22,792	11,396	25%
Medium	7,959	3,980	9%
Large	1,895	948	2%
C29 Manufacture of motor vehicles, trailers and semi-trailers Total	19,502	9,751	100%
Micro	12,149	6,075	62%
Small	3,836	1,918	20%
Medium	2,223	1,112	11%
Large	1,286	643	7%
C30 Manufacture of other transport equipment Total	14,653	7,326	100%
Micro	11,444	5,722	78%
Small	1,927	964	13%
Medium	869	435	6%
Large	413	207	3%
D35.1 Electric power generation, transmission and distribution Total	93,657	46828	100%
Micro	90,443	45,221	97%
Small	1,986	993	2%
Medium	762	381	1%
Large	466	233	0%
E38.1 Waste collection Total	20,121	10,060	100%
Micro	14,072	7,036	70%
Small	4,008	2,004	20%
Medium	1,626	813	8%
Large	415	207	2%
M72 Scientific research and development Total	62,560	31,280	100%
Micro	56,940	28,470	91%
Small	4,010	2,005	6%
Medium	1,280	640	2%
Large	330	165	1%
Total manufacturing	**1,059,233**	**529,618**	**-**
Total all sectors - all	**1,182,692**	**606,125**	**100%**
Total all sectors - micro	**954,216**	**486,920**	**81%**
Total all sectors - small	**166,001**	**86,082**	**15%**
Total all sectors - medium	**49,591**	**26,276**	**4%**
Total all sectors - large	**12,864**	**6,846**	**1%**
Source: Eurostat and RPA analysis *Notes: Some totals do not sum correctly due to rounding errors*			

X12.7.2 Number of enterprises in Member States with no OEL

Enterprises that are in Member States that already have an OEL are in a better position to incorporate any new OELV at EU level. They will have lower associated costs. Table X12-27 provides the percentage of enterprises in each sector that are in a Member State that does not have an OEL for boric acid. Table X12-28 provides the estimated no of exposed enterprises in MS without an OEL.

Table X12-27: Borate reprotoxins – percentage of enterprises in Member States without an OEL	
Sector	**% of enterprises in Member States without an OEL**
Chemicals and glass	
C20 Manufacture of chemicals and chemical products	29%
C23 Manufacture of other non-metallic mineral products (glass and ceramics)	33%
Manufacturing	
C10 Manufacture of food products	26%
C21 Manufacture of basic pharmaceutical products and pharmaceutical preparations	24%
C24 Manufacture of basic metals	28%
C25 Manufacture of fabricated metal products, except machinery and equipment	39%
C26 Manufacture of computer, electronic and optical products	28%
C27 Manufacture of electrical equipment	45%
C28 Manufacture of machinery and equipment n.e.c.	24%
C29 Manufacture of motor vehicles, trailers and semi-trailers	26%
C30 Manufacture of other transport equipment	27%
D35.1 Electric power generation, transmission and distribution	29%
E38.1 Waste collection	51%
M72 Scientific research and development	31%
Source: Eurostat and RPA analysis	

Table X12-28: Borate reprotoxins – number of enterprises and exposed enterprises split by size for Member States without OELs for boric acid for 2015			
Sector	**No of exposed enterprises**	**Enterprises in MS without an OEL %**	**Estimated no of exposed enterprises in MS without an OEL**
Chemicals and glass			
C20 Manufacture of chemicals and chemical products Total	14,778	29%	4,286
Micro	9,810	29%	2,845
Small	3,079	29%	893
Medium	1,477	29%	428
Large	413	29%	120
C23 Manufacture of other non-metallic mineral products (glass and ceramics)	46,952	33%	15,494

Table X12-28: Borate reprotoxins – number of enterprises and exposed enterprises split by size for Member States without OELs for boric acid for 2015			
Sector	**No of exposed enterprises**	**Enterprises in MS without an OEL %**	**Estimated no of exposed enterprises in MS without an OEL**
Total			
Micro	42,913	33%	14,161
Small	2,200	33%	726
Medium	1,460	33%	482
Large	371	33%	122
Total - chemicals and glass	**61,730**	**-**	**19,780**
Manufacturing			
C10 Manufacture of food products Total	132,927	26%	34,561
Micro	105,309	26%	27,380
Small	21,335	26%	5,547
Medium	5,082	26%	1,321
Large	1,201	26%	312
C21 Manufacture of basic pharmaceutical products and pharmaceutical preparations Total	2,091	24%	502
Micro	1,053	24%	253
Small	433	24%	104
Medium	369	24%	89
Large	235	24%	56
C24 Manufacture of basic metals	8,280	28%	2,318
Micro	5,189	28%	1,453
Small	1,807	28%	506
Medium	939	28%	263
Large	346	28%	97
C25 Manufacture of fabricated metal products, except machinery and equipment Total	192,202	39%	74,959
Micro	158,877	39%	61,962
Small	27,348	39%	10,666
Medium	5,338	39%	2,082
Large	640	39%	250
C26 Manufacture of computer, electronic and optical products Total	20,477	28%	5,734
Micro	15,364	28%	4,302
Small	3,506	28%	982
Medium	1,253	28%	351
Large	355	28%	99
C27 Manufacture of electrical equipment Total	23,380	45%	10,521
Micro	17,380	45%	7,821
Small	4,015	45%	1,807
Medium	1,520	45%	684
Large	470	45%	212
C28 Manufacture of machinery and equipment n.e.c. Total	45,014	24%	10,803

Table X12-28: Borate reprotoxins – number of enterprises and exposed enterprises split by size for Member States without OELs for boric acid for 2015			
Sector	**No of exposed enterprises**	**Enterprises in MS without an OEL %**	**Estimated no of exposed enterprises in MS without an OEL**
Micro	28,691	24%	6,886
Small	11,396	24%	2,735
Medium	3,980	24%	955
Large	948	24%	227
C29 Manufacture of motor vehicles, trailers and semi-trailers Total	9,751	26%	2,535
Micro	6,075	26%	1,580
Small	1,918	26%	499
Medium	1,112	26%	289
Large	643	26%	167
C30 Manufacture of other transport equipment Total	7,326	27%	1,978
Micro	5,722	27%	1,545
Small	963.5	27%	260
Medium	434.5	27%	117
Large	206.5	27%	56
D35.1 Electric power generation, transmission and distribution Total	46,828	29%	13,580
Micro	45,221	29%	13,114
Small	993	29%	288
Medium	381	29%	111
Large	233	29%	68
E38.1 Waste collection Total	10,060	51%	5,131
Micro	7,036	51%	3,588
Small	2,004	51%	1,022
Medium	813	51%	415
Large	207	51%	106
M72 Scientific research and development Total	31,280	31%	9,697
Micro	28,470	31%	8,826
Small	2,005	31%	622
Medium	640	31%	198
Large	165	31%	51
Total manufacturing	**529,618**	**-**	**172,320**
Total all sectors	**591,344**	**-**	**192,099**
Total all sectors - micro	**477,110**	**-**	**155,716**
Total all sectors - small	**83,003**	**-**	**26,656**
Total all sectors - medium	**24,798**	**-**	**7,785**
Total all sectors - large	**6,433**	**-**	**1,942**
Source: Eurostat and RPA analysis *Notes: Some totals do not sum correctly due to rounding errors*			

X12.7.3 Average turnover by size of enterprise

Table X12-29: Borate reprotoxins – average turnover by sector and size of enterprise, 2015												
Sector	Micro			Small			Medium			Large		
	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m
Chemicals and glass												
C20	13,281	19,580	0.68	34,247	6,240	6	132,655	2,950	45	346,366	830	417
C23	17,000	78,860	0.22	34,292	11,370	3	58,296	2,920	20	99,851	740	135
Manufacturing												
C10	57,030	207,260	0.28	140,842	44,540	3	273,000	10,160	267	490,000	2,400	204
C21	3,682	2,240	1.64	8,768	960	9	26,346	820	32	230,936	540	428
C24	5,600	10,240	0.55	22,615	3,640	6	71,133	1,880	38	242,830	690	352
C25	58,462	316,850	0.18	133,951	57,050	2	159,000	10,840	15	130,000	1,310	99
C26	11,316	30,230	0.37	24,040	7,000	3	51,321	2,510	20	200,000	700	285
C27	8,254	35,000	0.24	26,321	8,028	3	59,568	3,000	20	209,000	940	222
C28	23,157	57,395	0	80,592	23,129	3	165,774	7,923	21	387,695	1,900	204
C29	5,688	12,200	0.47	14,643	3,900	4	59,377	2,280	26	952,917	1,320	722
C30	5,183	11,454	0.45	7,319	1,974	4	19,849	900	22	180,382	419	431
D35.1	93,427	90,539	1	66,900	1,975	34	191,365	812	236	851,689	466	1,828
E38.1	6,191	15,304	0.40	9,227	3,194	3	14,786	1,413	10	28,467	317	90
M72	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Source: Eurostat's Structural Business Statistics database
Notes: Total number of enterprises differs slightly from ***Error! Reference source not found.*** *as data taken from different tables in Eurostat*

X12.7.4 Research & development expenditure

Table X12-30: Borate reprotoxins – business expenditure on R&D per sector (in € million), EU28		
Sector	**Data availability**	**R&D expenditure (in €m)**
Chemicals and glass		
C20	C20	6,659.7
C23	C23	881.7
Manufacturing		
C10	C10+C11	1,258.3
C21	C21	9,958.9
C24	C24	1,361.2
C25	C25	2,629.9
C26	C26	16,732
C27		
C28		
C29	C29	28,456.9
C30		
D35.1		
E38.1		
M72		
Source: Eurostat *Notes: EU28 totals do not include data for some member states, due to confidentiality.*		

X12.8 Burden of ill health

X12.8.1 Assumptions

The assumptions and calculations of exposed workers and children are as follows:

- From the IFA MEGA database, the highest 95 percentile exposure is 0.226 mg/m^3 in chemicals sector, this is well below any of the thresholds from the dose response relationship;
- The DNEL of boric acid converted to boron is 1.45 mg/m^3;
- The top 5 percentile of exposed workers is assumed to be exposed to 10 x DNEL of boric acid or 14.6 mg/m^3; and
- The remaining 95% of exposed workers are assumed to be exposed to levels below the thresholds.

X12.8.2 Effects leading to cases of ill-health

There are two endpoints with thresholds below the exposure level of 14.6 mg/m^3 which is being assumed for the top 5 percentile of exposed workers:

- Decrease in foetal body weight/litter
- Increased % malformed foetuses/litter (Visceral malformation)

Table X12-31: Reprotoxic borates – effects used for estimation, threshold, dose response relationship and % change for the top 5 percentile				
Monetisable effect	**Effect**	**Threshold mg/m^3**	**Dose response relationship**	**% change @14.6 mg/m^3**
Reduced foetal growth	Decrease in foetal body weight/litter	2.39	y=0.32x-0.7648	4%
Developmental abnormality	Increased % malformed foetuses/litter (skeletal malformation)	10.1	y=6.74x -68.074	30%

Table X12-31: Reprotoxic borates – effects used for estimation, threshold, dose response relationship and % change for the top 5 percentile				
Monetisable effect	**Effect**	**Threshold mg/m³**	**Dose response relationship**	**% change @14.6 mg/m³**
Source: RPA analysis				

X12.8.3 Children whom are potentially affected

Both of the possible effects involve children of women exposed to the top 5 percentile of and 2.83% of women of reproductive age (15-49) have children each year.

Table X12-32: Borate reprotoxins – number of female workers of reproductive age in the top 5 percentile experiencing the highest exposure levels and the number of births associated with them (1)		
Sector	**No of female workers reproductive age, 15-49 exposed to the highest levels (5%)**	**No of births to female workers of reproductive age / year exposed to the highest levels**
Chemicals and glass		
C20 Manufacture of chemicals and chemical products	136	4
C23 Manufacture of other non-metallic mineral products (glass and ceramics)	146	4
Total chemical and glass	**282**	**8**
Manufacturing		
C10 Manufacture of food products	1,057	30
C21 Manufacture of basic pharmaceutical products and pharmaceutical preparations	181	5
C24 Manufacture of basic metals	76	2
C25 Manufacture of fabricated metal products, except machinery and equipment	248	7
C26 Manufacture of computer, electronic and optical products	209	6
C27 Manufacture of electrical equipment	231	7
C28 Manufacture of machinery and equipment n.e.c.	200	6
C29 Manufacture of motor vehicles, trailers and semi-trailers	470	13
C30 Manufacture of other transport equipment	54	2
D35.1 Electric power generation, transmission and distribution	151	4
E38.1 Waste collection	18	1
M72 Scientific research and development	124	4
Total manufacturing	**3,019**	**85**
Source: Eurostat and RPA analysis *Notes: 1 Based upon a given percentage of the workforce in plant using boron, in Member States without an OEL*		

X12.8.4 Effect 1 - Decrease in foetal body weight/litter

The birth weights are categorised as follows:

- Low under 2.5 kg
- Very low under 1.5 kg
- Extremely low under 1 kg

For each of these categories, the percentage of births of all EU births that would be within 4% above the band was calculated and the process is described in Table X12-33. From this, it can be seen that 3.7% of all live births are between 2.5 and 2.6 kg and if subjected to a decrease in weight of 4% would be below 2 kg and thus move from being a normal body weight to a low body weight. The percentage of EU live births between 1.5 and 1.56 kg is 0.17% and would move from low to very low body weight with a 4% decrease in body weight. The percentage for very low to extremely low body weight is 0.05%.

Table X12-33: Borate reprotoxins –endpoint "decrease in foetal body weight/litter"			
Birth weight	**Extremely low**	**Very low**	**Low**
Definition	< 1.0 kg	1.0 - 1.5 kg	1.5 - 2.5 kg
Definition of band above	1.0 - 1.5 kg	1.5 - 2.0 kg	2.5 - 3.0 kg
Births in band above in 2015 (1)	31,991	72,768	944,468
Range in which a 4% decrease would move the birth to a lower weight	1.0 - 1.04 kg	1.5 - 1.56 kg	2.5 - 2.6 kg
Difference between top and bottom of the range	0.04 kg	0.06 kg	0.1 kg
Difference as % of the 0.5 kg band	8%	12%	20%
Number of births in EU in the band above in 2015	2,559	8,732	188,894
Number of births in EU in band above as % of total number of births in EU in 2015 (5.1 million)	0.05%	0.17%	3.7%
Source: Eurostat: Live births by birth weight and duration of gestation, RPA analysis *Notes: 1 based on Eurostat data for BG, CZ, IE, EL, ES, LT, HU, MT, PO, PT, RO, SK, FI, extrapolated for EU*			

X12.8.5 Effect 2 - Increased % malformed foetuses/litter, visceral malformation

This effect is expected to lead to many possible skeletal malformations and the prevalence of these is between 0.1 and 0.6% of births.

An increase of 30% in this rate of defects, leads to an increase of between 0.03 and 0.18% of births with these effects. The worst-case scenario of the highest prevalence leading to a 0.18% increase of births with these effects is taken in the calculation of cases of ill-health.

X12.8.6 Cases of ill health

The cases of ill-health resulting from the two endpoints are presented in the table below.

Table X12-34: Borate reprotoxins – number of cases arising per year from ill-health effects – worst case scenario based upon top 5 percentile of exposed workers receiving exposure of 10 x DNEL						
Sector	**Exposed female workers**	**Births per exposed female worker /year**	**Cases/year due to Decrease in foetal body weight/litter Normal to low body weight**	**Cases/year due to Decrease in foetal body weight/litter Low to very low body weight**	**Cases/year due to Decrease in foetal body weight/litter Very low to extremely low body weight**	**Cases/year due to Increased % malformed foetuses/litter (skeletal malformation)**
Chemicals and glass						
C20 Manufacture of chemicals and chemical products	136	4	0.157	0.007	0.003	0.007
C23 Manufacture of other non-metallic mineral products (glass and ceramics)	146	4	0.157	0.007	0.003	0.007
Total for chemicals and glass	**282**	**8**	**0.314**	**0.014**	**0.004**	**0.016**
Manufacturing						
C10 Manufacture of food products	1,057	30	38.85	1.8	0.55	1.89
C21 Manufacture of basic pharmaceutical products and pharmaceutical preparations	181	5	7.4	0.35	0.1	0.36
C24 Manufacture of basic metals	76	2	3.7	0.15	0.05	0.18
C25 Manufacture of fabricated metal products, except machinery and equipment	248	7	9.25	0.45	0.15	0.45
C26 Manufacture of computer, electronic and optical products	209	6	7.4	0.35	0.1	0.36
C27 Manufacture of electrical equipment	231	7	9.25	0.45	0.15	0.45
C28 Manufacture of machinery and equipment n.e.c.	200	6	7.4	0.35	0.1	0.36
C29 Manufacture of motor vehicles, trailers and semi-trailers	470	13	16.65	0.75	0.25	0.81
C30 Manufacture of other transport equipment	54	2	1.85	0.1	0.05	0.09
D35.1 Electric power generation, transmission and distribution	151	4	5.55	0.25	0.1	0.27
E38.1 Waste collection	18	1	0	0	0	0
M72 Scientific research and development	124	4	5.55	0.25	0.1	0.27
Total for manufacturing	**3,019**	**85**	**112.85**	**5.25**	**1.7**	**5.49**
TOTAL	**3,301**	**93**	**123.95**	**5.75**	**1.85**	**6.05**

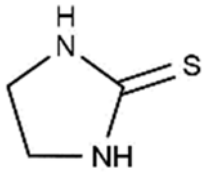
Table X12-34: Borate reprotoxins – number of cases arising per year from ill-health effects – worst case scenario based upon top 5 percentile of exposed workers receiving exposure of 10 x DNEL						
Sector	Exposed female workers	Births per exposed female worker /year	Cases/year due to Decrease in foetal body weight/litter Normal to low body weight	Cases/year due to Decrease in foetal body weight/litter Low to very low body weight	Cases/year due to Decrease in foetal body weight/litter Very low to extremely low body weight	Cases/year due to Increased % malformed foetuses/litter (skeletal malformation)
Source: RPA analysis						

Annex 13 Imidazolidine-2-thione (ETU)

X13.1 Introduction

X13.1.1 Relevant substance

Imidazolidine-2-thione or Ethylene thiourea (ETU) is an industrial chemical as well as a degradation product of ethylenebisdithiocarbamates (EBDC) fungicides. Synonyms are 2-imidazolidine-2-thione, 2-imidazolidinethione, 2-imidazoline-2-thiol, 2-mercaptoimidazoline, 1,3-ethylene-2-thiourea, 1,3-ethylenethiourea, 2-mercaptoimidazoline, and mercaptoimidazoline[480,481,482]. Trade names of ETU include Ekaland ETU, ETU, Mixland ETU, Uhoo ETU. When heated to decomposition, ETU emits toxic fumes of nitrogen oxides and sulphur oxides[483].



Ethylene Thiourea (ETU); CAS No.: 96-45-7; EC No.: 202-506-9; Molecular Formula: $C_3H_6N_2S$[480]

ETU was registered under REACH within the tonnage band 100–1,000 tons per annum and the registered uses are as a vulcanisation agent (as such or in mixtures) in the production of GRGs (General Rubber Goods) and tyres[484]. It occurs as white to pale green needle-like crystals with a faint amine odour.

X13.1.2 Hazard classification(s)

ETU has harmonised classification, under annex VI of regulation (EC) No 1272/2008 (CLP regulation), as Acute Tox. 4 and Repr 1B. Details of this classification, along with other notified classification and labelling, according to CLP criteria, are listed in A12-1.

[480] ChemIDplus, A TOXNET database, Ethylene thiourea, CAS No. 96-45-7 https://chem.nlm.nih.gov/chemidplus/rn/96-45-7 (Accessed on 17 May 2018).

[481] ECHA (no date) *Imidazolidine-2-thione registration dossier*. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/13536 (Accessed: 26 July 2018).

[482] PubChem (no date) *2-mercaptoimidazoline*. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/2-Imidazolidinethione#section=Top (Accessed: 26 July 2018).

[483] Leonard B, editor. Eighth Annual Report on Carcinogens. Diane Publishing; 1999. Available in Google books. https://books.google.co.in/books?id=uAP7svih6pEC&pg=PA122&dq=ethylene+thiourea&hl=en&sa=X&ved=0ahUKEwjxxNybr4fbAhVCvI8KHbznCjEQ6AEIVzAJ#v=onepage&q=ethylene%20thiourea&f=false

[484] Annex XV-IDENTIFICATION OF IMIDAZOLIDINE-2-THIONE (2-IMIDAZOLINE-2-THIOL) AS SVHC, Submitted by: Swedish Chemicals Agency. https://echa.europa.eu/documents/10162/13640/ec_202_506_9_imidazolidine_annex_xv_svhc_pub.pdf

Table X13-1: Hazard classification for ETU		
Hazard class and category code	**Hazard statement code**	**Explanation**
Harmonised classification – Annex VI of regulation (EC) No 1272/2008 (CLP regulation)		
Acute Tox. 4	H302	Harmful if swallowed
Repr. 1B	**H360D**	**May damage the unborn child**
Notified classification and labelling according to CLP – lead dossier of REACH registration joint submission		
Acute Tox. 4	H302	Harmful if swallowed
Repr. 1B	**H360**	**May damage fertility or the unborn child**
Acute Tox. 4	H302	Harmful if swallowed
Carc. 2	H351 (oral)	Suspected of causing cancer (Target organs: thyroid and liver)
Repr. 1B	**H360**	**May damage fertility or the unborn child**
STOT RE 1	H372 (Thyroid)	Causes damage to organs through prolonged or repeated exposure (Affected organs: thyroid)

X13.1.3 Existing OELs, BLVs and DNELs

Existing OELs and BLVs for imidazolidine-2-thione are listed in Table X13-2. An OEL could only be found for Finland and Poland, and despite harmonised classification as Acute Tox. 4 and Repr. 1B, there is no listed harmonised EU OEL. No biological limit values (BLVs) could be found for any member states or for the EU.

Table X13-2: Summary of existing OELs and BLVs in EU countries and key non-EU countries	
Country	**OEL (mg/m^3)**
Finland	0.1
The Netherlands	0.024 (recommended)
Poland	0.1
Source: (Health Council of the Netherlands, 1999)	

DNEL (Derived No Effect Level)[485]

DNEL for workers via inhalation route

The occupational long term DNEL for worker inhalation hazard for repeated dose toxicity is set at 0.07 mg/m^3, including an overall assessment factor of 75, or 5.25 mg/m^3 without consideration of the assessment factor.

DNEL for workers via dermal route

The occupational long term DNEL for worker dermal hazard is set at 1.7 mg/kg bw/day, including overall assessment factor of 100 rated for repeated dose toxicity.

[485] ECHA Dossier for Imidazolidine-2-thione. https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/13536/7/1

X13.1.4 Legislation other than CAD

This substance is not restricted or authorised under REACH.[486]

X13.2 Summary of health endpoints, thresholds and DRRs

X13.2.1 Relevant health endpoints

Relevant reproductive health endpoints

Given its CLH hazard classification, Repr. 1B H360D, ETU may damage the unborn child. Relevant reproductive health endpoints, identified from literature review, are given in Table X13-3, along with a monetised health effect that may be used to value it.

Literature review was undertaken to identify all potentially relevant effects. Those identified were all derived from animal studies and no human studies with relevant data were found. Relevant effects were grouped according to their effects on the reproductive system and embryonic/foetal development. A general no-effect threshold in humans was derived, along with a slope of a dose-response curve. The potential effects are presented in Table X13-3 for those effects that are relevant to human reproductive and developmental health.

Table X13-3: ETU – summary of reproductive health effects

Health effects	Fertility/ development		Male/ Female exposure	Monetisable effect correlate
	Fer	Dev		
Decrease in iodine uptake in male[487]		Dev	M	Impaired or reduced fertility – male
Decreased percent of T-3 bound to thyroxine-binding globulin (TBG)-male[487]		Dev	M	Impaired or reduced fertility – male
Decreased serum T-4 level-male[487]		Dev	M	Impaired or reduced fertility – male
Decreased serum T-3 level-male[487]		Dev	M	Impaired or reduced fertility – male
Increase in thyroid-to-body-weight ratio[487]		Dev	M	Impaired or reduced fertility – male
Decreased percent of T-3 bound to thyroxine-binding globulin (TBG)-female[487]		Dev	F	Impaired or reduced fertility – female
Decreased serum T-3 level-female[487]		Dev	F	Impaired or reduced fertility – female
Decreased serum T-4 level-female[487]		Dev	F	Impaired or reduced fertility – female
Decrease in iodine uptake[488]		Dev	F	Impaired cognitive development

[486] https://echa.europa.eu/substance-information/-/substanceinfo/100.002.280

[487] Freudenthal RI et al, 1977. Dietary subacute toxicity of ethylenethiourea in laboratory rat. J. Environ. Pathol. Toxicol. 1: 147-161. As cited in ECHA dossier for Imidazolidine-2-thione. https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/13536/7/6/2

[488] Graham SL and Hansen WH. Effects of short-term administration of ethylene-thiourea upon thyroid function of the rat. Bull. Environ. Contam. Toxicol. 7: 19-25. As cited in ECHA dossier for Imidazolidine-2-thione. https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/13536/7/6/2/?documentUUID=96f2557e-ccc9-46f7-85f1-a188d61bfb05

Table X13-3: ETU – summary of reproductive health effects				
Health effects	Fertility/ development		Male/ Female exposure	Monetisable effect correlate
	Fer	Dev		
Increase in resorption sites and dead foetuses (mean/litter)[489]		Dev		Spontaneous abortion or still birth
Decreased mean no. of live foetuses[490]		Dev		Spontaneous abortion or still birth
Increase in % foetal death[490]		Dev		Spontaneous abortion or still birth
Decrease in mean no. of foetuses[491]		Dev	F	Spontaneous abortion or still birth
Increased incidence of foetal death[490]		Dev	F	Spontaneous abortion or still birth
Decrease in male foetal body weight per litter[492]		Dev	F	Reduced foetal growth
Decrease in female foetal body weight per litter		Dev	F	Reduced foetal growth
Decrease in mean foetal weight[492]		Dev	F	Reduced foetal growth
Decrease in foetal body weights-male[490]		Dev	F	Reduced foetal growth
Decrease in foetal body weights-female[490]		Dev	F	Reduced foetal growth
Decrease in foetal weight[491]		Dev	F	Reduced foetal growth
Decrease in foetal Crown-Rump length[491]		Dev	F	Reduced foetal growth
Increased incidence of dumbbell-shaped or blobbed vertebral centra[492]		Dev	F	Spina bifida
Increased incidence of cranial meningocele[492]		Dev	F	Spina bifida
Increased incidence of cranial meningorrhea[492]		Dev	F	Spina bifida
Increased incidence of severe hind limb talipes[492]		Dev	F	Skeletal effects or abnormalities of the limbs
Increased incidence of short and/or kinky tail[492]		Dev	F	Skeletal effects or abnormalities of the limbs
Increased incidence of short or kinky tail[490]		Dev	F	Skeletal effects or abnormalities of the limbs
Increased incidence of tail anomalies[491]		Dev	F	Skeletal effects or abnormalities of the limbs
Increased incidence of dilated brain ventricles[492]		Dev	F	Developmental neuro-impairment
Increased incidence of hydro ureter[492]		Dev	F	Renal abnormalities

[489] Khera et. al. 1973. Ethylenethiourea: teratogenicity study in rats and rabbits. Teratology, 7 : 243-252 (As sited in ECHA dossier for Imidazolidine-2-thione). https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/13536/7/9/3/?documentUUID=8c1db47f-90e6-4dd3-893b-0f0a4a96e7e6

[490] Teramoto et. al. 1978. Teratogenicity studies with ethylenethiourea in rats, mice and hamsters. Cong. Anom., 18: 11-17 (As sited in ECHA dossier for Imidazolidine-2-thione). https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/13536/7/9/3/?documentUUID=c6690f2b-52eb-4e7a-af1d-b57ac05b08ab

[491] Hirai et. al. 1990. Transplacentally induced anorectal malformations in rats. J. Pediatr. Surg. 25: 812-816 (As sited in ECHA dossier for Imidazolidine-2-thione). https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/13536/7/9/3/?documentUUID=83d40652-b908-4d78-ba14-044af6c5a8cd

[492] Saillenfait et. al. 1991. Difference in the developmental toxicity of ethylenethiourea and three N,N-substituted thiourea derivatives in rats. Fundam. Appl. Toxicol. 17: 399-408 (As sited in ECHA dossier for Imidazolidine-2-thione). https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/13536/7/9/3/?documentUUID=d8ffe127-6162-48c6-ab4b-ba9470f4303a

Table X13-3: ETU – summary of reproductive health effects				
Health effects	Fertility/ development		Male/ Female exposure	Monetisable effect correlate
	Fer	Dev		
Increased incidence of dilated ureter[492]		Dev	F	Renal abnormalities
Increase in % total malformed foetuses[489]		Dev	F	Foetal anomaly
Increase in total activity score (F1)[493]		Dev	F	Attention deficit disorder

The first nine effects in Table X13-3 relate to thyroid effects, which cannot be quantified in humans. However, the last of these nine effects relates to a reduction in iodine uptake by females and there is separate research linking low urinary iodine concentration in pregnant women to reductions in the IQ of offspring and this effect is retained.

X13.2.2 Other health endpoints

Other than reproductive toxicity, experimental data reported in the registration dossier, describes carcinogenic effects in animal experiments. The results reported are focussed on thyroid toxicity, with significant increases in the incidence of thyroid follicular cell tumours reported in male and female rats, at an oral exposure of 83–250 ppm, with or without perinatal exposure. This is supported by further experimental evidence in rats, and histological thyroid hyperplasia was observed at lower oral doses, of around 5–24 ppm

Table X13-4 shows some maternal health effects that were seen in the studies.

Table X13-4: ETU – summary of maternal health effects	
Health effects	Threshold (converted) (mg/m^3)
Decrease in spleen-to-body-weight ratio[487]	14.0
Increase in brain-to-body-weight ratio[487]	14.0
Increase in kidneys-to-body-weight ratio[487]	14.0
Increase in pituitary-to-body-weight ratio[487]	14.0

X13.2.3 Summary of thresholds and DRRs

Table X13-5: Selected Occupational endpoints: Thresholds and dose response					
Effects		Threshold		Dose response curve	
		Converted (mg/m^3)	Range of Applicability for Slope	Converted (mg/m^3)	Slope ($\%/mg/m^3$)
Impaired cognitive development	Decrease in iodine uptake	4.38	8.76	4.38	-2.99
Spontaneous abortion or still birth	Increase in resorption sites and dead foetuses (mean/litter)	117	234	117	0.21
	Decreased mean no. of live foetuses	378	1134	756	-0.03
	Increase in % foetal death	378	1134	756	0.03

[493] Chernoff et. al. 1979. Perinatal toxicity of maneb, ethylene thiourea, and ethylenebisisothiocyanate sulfide in rodents. J Toxicol. Environ. Health 5: 821-834 196 (As sited in ECHA dossier for Imidazolidine-2-thione). https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/13536/7/9/3/?documentUUID=4337ec46-4caa-4b39-93e4-17225e06f1d5

Table X13-5: Selected Occupational endpoints: Thresholds and dose response					
Effects		Threshold		Dose response curve	
		Converted (mg/m^3)	Range of Applicability for Slope	Converted (mg/m^3)	Slope ($\%/mg/m^3$)
	Decrease in mean no. of foetuses	17.5	175.5	158	-0.19
	Increased incidence of foetal death	70.0	87.5	17.5	2.79
Reduced foetal growth	Decrease in male foetal body weight per litter	43.8	61.3	17.5	-0.72
	Decrease in female foetal body weight per litter	43.8	61.3	17.5	-0.86
	Decrease in mean foetal weight	35.0	70	35.0	-0.70
	Decrease in foetal body weights-male	35.0	52.5	17.5	-0.46
	Decrease in foetal body weights-female	35.0	52.5	17.5	-0.50
	Decrease in foetal weight	263	350.5	87.5	-0.11
	Decrease in foetal Crown-Rump length	17.5	175.5	158	-0.05
Spina bifida	Increased incidence of dumbbell-shaped or blobbed vertebral centra	43.8	61.3	17.5	16.5
	Increased incidence of cranial meningocele	43.8	61.3	17.5	1.37
	Increased incidence of cranial meningorrhea	43.8	61.3	17.5	0.69
Skeletal effects or abnormalities of the limbs	Increased incidence of severe hind limb talipes	43.8	61.3	17.5	2.16
	Increased incidence of short and/or kinky tail	43.8	61.3	17.5	2.61
	Increased incidence of short or kinky tail	30	47.5	17.5	5.7
	Increased incidence of tail anomalies	17.5	175.5	158	0.63
Developmental neuro-impairment	Increased incidence of dilated brain ventricles	26.3	43.8	17.5	2.22
Renal abnormalities	Increased incidence of hydro ureter	43.8	61.3	17.5	0.72
	Increased incidence of dilated ureter	43.8	61.3	17.5	0.72
Foetal anomaly	Increase in % total malformed foetuses	35.0	105	70.0	1.19
ADHD	Increase in total activity score (F1)	43.8	52.55	8.75	4.19

X13.3 Relevant sectors, uses, and operations

ETU is used principally as an accelerator for vulcanising chloroprene (polychloroprene, neoprene) and polyacrylate rubbers. Neoprene rubbers are used in numerous articles almost exclusively in industrial applications such as for mechanical and automotive products, in wire and cable production, in construction and in adhesives. Polyacrylate rubbers are used in products such as seals, o-rings and

gaskets for automotive and aircraft applications[494]. ETU is also used as a curing agent for epichlorohydrin elastomers.[495]

ETU is a metabolite, degradation product and (cooking) by-product of the manufacture of ethylene bisdithiocarbamates (EBDC) pesticides, such as mancozeb, metiram and nabam[496] [497]. Nabam is not approved for use in the EU, under regulation (EC) no 1107/2009; mancozeb is approved under regulations (EU) No 84/2018, (EU) No 540/2011, (EU) No 762/2013 (05/72/EC); metiram is approved under regulations 05/72/EC, (EU) No 540/2011, (EU) No 762/2013, (EU) No 84/2018[498]. Metiram is considered to have moderate acute toxicity. It is not significantly absorbed through the skin. Of the EBDC members, nabam shows the greatest toxicity, probably due to its greater water solubility and absorbability. The ETU content in EBDC fungicides depends on the pesticide storage conditions, and increases with temperature, moisture and length of storage[499].

ETU is also used in electroplating baths, as an intermediate in antioxidant production, in dyes, pharmaceuticals and synthetic resins.[496]

In the consultation, the only response from a company with ETU handling workers was from the rubber manufacturing sector, but only the basic information was completed.

In conclusion, there are four sectors in which workers are potentially exposed to ETU[500]:

1. ETU manufacturing;
2. Enterprises engaged in the production of synthetic rubber for which ETU is used as a curing accelerator or vulcanising agent;
3. EBDC manufacturing;
4. Agricultural workers and farmers, using EBDCs to protect crops.

Table X13-6 summarises these sectors in which ETU is used, according to NACE code. Table X13-7 summarises the uses by PROC code, as reported in the ECHA registration dossier. Registration dossiers for EBDCs are not available, so there are no process indicators for their manufacture and use.

[494] ToxNet (no date) *Ethylene thiourea*, *US National Library of Medicine*. Available at: https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+1643 (Accessed: 26 July 2018)

[495] PubChem (no date) *2-mercaptoimidazoline*. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/2-Imidazolidinethione#section=Top (Accessed: 26 July 2018).

[496] Kurttio, P. and Savolainen, K. (1990) 'Ethylenethiourea in air and in urine as an indicator of exposure to ethylenebisdithiocarbamate fungicides', *Scandinavian Journal of Work, Environment and Health*, 16(3), pp. 203–207. doi: 10.5271/sjweh.1793

[497] USEPA, Reregistration Eligibility Decision (RED) for Maneb 2005. https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-014505_1-Aug-05.pdf

[498] European Commision (2018) *EU - Pesticides database*. Available at: http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=homepage&language=EN (Accessed: 20 July 2018).

[499] National Toxicology Program (2016) *Ethylene Thiourea: 14th report on carcinogens*, *Organic Syntheses*. doi: 10.15227/orgsyn.026.0034.

[500] Health Council of the Netherlands (1999) *Dutch Expert Committee on Occupational Standards (DECOS). Ethylene thiourea*. The Hague. Available at: https://www.gezondheidsraad.nl/sites/default/files/osh03.pdf

There is no available information on the use of ETU in dyes, pharmaceuticals, synthetic resins, and electroplating baths, and it can therefore be assumed that its use in these sectors is negligible, so will not be included in this analysis.

According to analytical data, the residual ETU in an article of mercaptan-modified chloroprene rubber is from 0.0007% to 0.0035% and in an article of sulphur-modified chloroprene rubber it is 0.0297% to 0.0783%. Given the market constitution of these two types of chloroprene rubber, the weighted average of the residual ETU in all chloroprene articles is approximately 0.01%[501]. The use of ETU by down-stream manufacturers producing products such as cables is, therefore, not expected to generate significant exposure levels. Furthermore, studies have shown that rubber masterbatches do not generate hazardous volatile dusts under mechanical wear[501]. These will therefore be excluded from the analysis.

Table X13-6: ETU – sectors and uses		
Sector[502,503,504]	**Uses and/or activities**	**NACE code**
Manufacture of other basic organic basic chemicals	Production of ETU	C20.1.4
Manufacture of rubber tyres and tubes; re-treading and rebuilding of rubber tyres	Used as a vulcanisation agent in the production of rubber goods and tyres	C22.11
Manufacture of other rubber products	Used as a vulcanisation agent in the production of rubber goods and tyres	C22.19
Manufacture of pesticides and other agrochemical products	Production of EBDC	C20.2
Agriculture – growing of non-perennial crops	EBDC use, as fungicide – ETU as degradation product	A1.1
Agriculture – growing of perennial crops	EBDC use, as fungicide – ETU as degradation product	A1.2
Silviculture and other forestry activities	EBDC use, as fungicide – ETU as degradation product	A2.1
Manufacture of basic metals	Used in electroplating baths	C24
Source: RPA research		

[501] ECHA (2013) *COMMENTS ON AN ANNEX XV DOSSIER FOR IDENTIFICATION OF A SUBSTANCE AS SVHC AND RESPONSES TO THESE COMMENTS*. Available at: http://echa.europa.eu/documents/10162/49cb5b89-169e-471d-a0b8-97dceb7ed0ee.

[502] https://echa.europa.eu/documents/10162/13640/ec_202_506_9_imidazolidine_annex_xv_svhc_pub.pdf

[503] https://www.sciencedirect.com/science/article/pii/S1350417707000478

[504] Industry association consultation response

Table X13-7: Use descriptors for identified uses of ETU	
Area	**Process category (PROC)**
Manufacture and formulation	
Manufacture of substance as vulcanisation agent in powder (containing ETU) (Ekaland)	PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing) PROC 15: Use as laboratory reagent PROC 21: Low energy manipulation of substances bound in materials and/or articles
Manufacture of polymer-bound master batches of vulcanisation agents (inc. ETU) (Mixland)	PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing) PROC 14: Tabletting, compression, extrusion, pelletisation, granulation PROC 15: Use as laboratory reagent PROC 21: Low energy manipulation of substances bound in materials and/or articles PROC 24: High (mechanical) energy work-up of substances bound in materials and/or articles
Industrial formulation of a pre-dispersed preparation of ETU	PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 10: Roller application or brushing PROC 14: Production of preparations or articles by tabletting, compression, extrusion, pelletisation PROC 21: Low energy manipulation of substances bound in materials and/or articles
Uses at industrial sites	
Industrial use as vulcanising agent – in tyres	PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 10: Roller application or brushing PROC 14: Tabletting, compression, extrusion, palletisation, granulation PROC 21: Low energy manipulation of substances bound in materials and/or articles

Table X13-7: Use descriptors for identified uses of ETU	
Area	**Process category (PROC)**
Industrial use as vulcanising agent – in GRG	PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 7: Industrial spraying PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 10: Roller application or brushing PROC 13: Treatment of articles by dipping and pouring PROC 14: Tabletting, compression, extrusion, palletisation, granulation PROC 21: Low energy manipulation of substances bound in materials and/or articles
Manufacture of metals, including alloys - Anti-corrosion	PROC 4: chemical production where opportunity for exposure arises PROC 5: Mixing or blending in batch process PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities
Source: ECHA (no date) Imidazolidine-2-thione registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/13536 (Accessed: 26 July 2018)	

X13.4 Exposed workforce

No information about exposed workers was found in the SUMER[505], GESTIS[506] or ASA[507] databases for this substance.

X13.4.1 Total number of exposed workers

Estimates identified through literature review and consultation for this study

Literature review has revealed no direct evidence of the number of workers exposed (or potentially exposed) to ETU in the EU. The exposed workforce can, however, be estimated, for the purposes of this study, based on employment figures indirectly related to ETU, and a number of assumptions based on available data. The evidence is outlined below and the assumptions, based on this, are summarised in Table X13-8, along with the number of workers in each sector.

Manufacturing of ETU

"The manufacturing impurity ETU is considered to be of toxicological concern and must not exceed 0.5% of the active substance."[508]

[505] France: Working conditions and occupational risks: SUMER 2010 https://www.eurofound.europa.eu/publications/article/2013/france-working-conditions-and-occupational-risks-sumer-2010

[506] IFA Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (2017): GESTIS - Internationale Grenzwerte für chemische Substanzen. Available at: http://www.dguv.de/ifa/GESTIS/GESTIS-Internationale-Grenzwerte-für-chemische-Substanzen-limit-values-for-chemical-agents/index.jsp

[507] ASA Finland Institute of Occupational Health (2014): Those who cause cancer substances and methods in their profession exposed in Finland. Available at: https://www.julkari.fi/handle/10024/131073

[508] European Commision (2005) *Review report for the active substance metiram*

Manufacturing of rubber products

Vulcanisation of chloroprene rubber is a relatively specialised application, resulting in a low number of people involved in ETU-handling within the EU.

ETU is used less than 20 days/year, i.e. less than 4% of the work-time per year[501].

Some down-stream users use ETU for manufacturing masterbatches. The ETU is then consumed in the next steps of the supply-chain, as part of the General Rubber Goods (GRG) industry[501].

According to analytical data, the residual ETU in an article of mercaptan-modified chloroprene rubber is from 0.0007% to 0.0035% and in an article of sulphur-modified chloroprene rubber it is 0.0297% to 0.0783%. Given the market constitution of these two types of chloroprene rubber, the weighted average of the residual ETU in all chloroprene articles is approximately 0.01%[501].

If we assume that 300,000 metric tons of chloroprene rubber are consumed annually; ETU is added to 50% of the annually consumed chloroprene rubber (other accelerators used, or applications not needing vulcanisation); and 1% ETU is added to chloroprene rubber; then the annual world-wide consumption of ETU would be approximately 1,500 metric tons. If chloroprene rubber articles contain approximately 0.01% ETU, then the world-wide volume of residual ETU in chloroprene articles is only 0.15 metric tons. Workers involved on the manufacture of chloroprene rubber articles after the vulcanisation process are exposed to negligible amounts of ETU[501].

Manufacturing of EBDC

Agricultural use of EBDC (ETU as degradation product)

Table X13-8: Estimated exposed workforce by sector – women of reproductive age (15–49)

Sector	Assumptions	Estimated no. of female workers of reproductive age (15–49)
Manufacture of chemicals and chemical products	• 307,400 women of reproductive age working in manufacture of chemicals and chemical products • 30% of C20 enterprises are C20.1 • 10% chemical manufacturing plants are manufacturing ETU • 20% of workers in enterprises manufacturing ETU are exposed to ETU	1,804
Manufacture of rubber products	• 324,971 workers in rubber manufacturing • 90% of rubber manufacturers produce chloroprene rubber • 50% of enterprises producing chloroprene rubber, are using ETU as an accelerating agent. • 20% of workers within these enterprises are exposed to ETU • 10% of workers are women of reproductive age	2,924
Manufacture of pesticides and other agrochemicals	• 307,400 women of reproductive age working in manufacture of chemicals and chemical products • 2.1% of C20 enterprises are C20.2 • 20% chemical manufacturing plants are manufacturing EBDC 50% of workers in enterprises manufacturing EBDC are exposed to EBDC and its bi-products	631

Table X13-8: Estimated exposed workforce by sector – women of reproductive age (15–49)		
Sector	**Assumptions**	**Estimated no. of female workers of reproductive age (15–49)**
Agriculture	• 1,645,500 women of reproductive age working in agriculture – crop and animal production, hunting and related activities. • 50% of farms involved in crop production • 50% of farms using EBDC. • 10% of workers within these farms are involved in activities where exposure to EBDC and its bi-products is possible	41,138
Sources: Eurostat		

Trends

There is likely to be a downward trend in the use of ETU as an accelerator for the vulcanisation of chloroprene rubber. This is due to research into a viable alternative,[509] which was found and has been shown to perform as well, if not better than, ETU, without the toxicity. This is particularly beneficial to SMEs, which are particularly hard hit by regulatory restriction and rising competition from countries with less stringent health and safety requirements.

X13.5 Exposure levels

X13.5.1 Exposure routes

The routes of potential human exposure are inhalation, ingestion and dermal contact[510].

X13.5.2 Current exposure levels

Manufacturing ETU and rubber products

An occupational exposure study was conducted on male workers in two different factories in the UK. ETU was manufactured at one factory (Factory 1) and mixed into masterbatch rubber at another (Factory 2)[511]. In 1976, concentration measurements were carried out. The concentration of ETU dust was between 0.010 and 0.240 mg/m^3, ranging up to 0.330 mg/m^3. In Factory 2, sampled in 1980, concentrations in personal samplers ranged from 0.120 to 0.160 mg/m^3.

Manufacturing EBDC

Among workers in Italy producing commercial formulations of mancozeb, the urinary concentration of ETU was highest in those formulating pesticide in powdered form (median = 55.4 µg/g of creatinine), reflecting the higher concentrations found in the air (1.9 µg/m^3), in the hand-wash residue

[509] SafeRubber. https://cordis.europa.eu/project/rcn/96346_en.html

[510] National Toxicology Program (2016) *Ethylene Thiourea: 14th report on carcinogens*, *Organic Syntheses*. doi: 10.15227/orgsyn.026.0034.

[511] Smith DM, Ethylene thiourea: thyroid function in two groups of exposed workers Br J Ind Med. 1984 Aug;41(3):362-6.

(36.9 to 194.3 µg), and in pads attached to the workers' necks (15 to 96 ng/cm^2) in the area of the plant where the pesticide powder was formulated.[512,510]

Agricultural use of EBDC (ETU as degradation product)

ETU is one of the principal residues found in plants and in the environment following agricultural use of EBDCs. ETU is also a metabolite formed when EBDCs are ingested by animals and man.

In an environmental monitoring study (reported in 1999) of potato field and pine nursery workers in Finland, air samples were collected from the breathing zones of the workers throughout the working period and while the pesticide (maneb, manganese salt of EBDC) was being weighed. The average ETU concentrations in the breathing zones were 0.14 and 0.60 mg/m^3 for potato field and pine nursery workers respectively. During weighing, the corresponding airborne ETU levels were 0.87 and 1.81 mg/m^3.[513] Here the ETU concentrations exceed the thresholds in our study, by at least one order of magnitude above the DNEL.

A study was performed at 14 potato farms in Finland (reported in 1990) in which air samples were collected from the breathing zones of farmers and from the cabins of their tractors. The airborne concentrations of ETU ranged between 0.004 and 3.3 mg/m^3 in the breathing zones and between 0.006 and 0.8 mg/m^3 in the tractor cabins. Given the two to three orders of magnitude range, some of the effects in our study will have thresholds lower than the upper boundaries reported here.

Among agricultural workers in Italy, who regularly handled EBDC pesticides, pre-exposure urinary concentrations ranged from 0.5 to 2.1 µg/L and post-exposure concentrations from 1.9 to 8.2 µg/L.[514] In another study in Italy, workers had pre-exposure concentrations of less than 1.6 µg/g of creatinine and a post-exposure median concentration of 8.5 µg/g, with a maximum of 40.1 µg/g.[515] A third study in Italy confirmed these findings.[516,510]

Table X13-9: Exposure to ETU

Sector/use	Country	Study	Air concentration	Urine
ETU manufacture	UK	Smith et al. (1984)[511]	0.010–0.240 mg/m^3 (up to 0.330 mg/m^3)	
ETU mixed into masterbatch	UK	Smith et al. (1984)[511]	0.120–0.160 mg/m^3	
Manufacture of EBDCpesticide. Formulating in powdered form.	Italy	Aprea et al. (1998)[512]	1.9 µg/m^3	Median = 55.4 µg/g of creatinine

[512] Aprea, C. *et al.* (1998) 'Environmental and biological monitoring of exposure to mancozeb, ethylenethiourea, and dimethoate during industrial formulation', *J Toxicol Environ Health A.*

[513] Savolainen K, Kurttio P, Vartianen T, et al. Ethylene thiourea as an indicator of exposure to ethylenebisdithiocarbamate fungicides. Arch Toxicol 1989, (suppl 13): 120-3 as cited in Health Council of the Netherlands: Dutch Expert Committee on Occupational Standards (DECOS), Ethylene thiourea, (1999).

[514] Sottani, C. *et al.* (2003) 'Analytical method for the quantitative determination of urinary ethylenethiourea by liquid chromatography/electrospray ionization tandem mass spectrometry', *Rapid Communications in Mass Spectrometry*. Wiley-Blackwell, 17(20), pp. 2253–2259. doi: 10.1002/rcm.1171.

[515] Fustinoni, S. *et al.* (2005) 'Application of gas chromatography-mass spectrometry for the determination of urinary ethylenethiourea in humans', *Journal of chromatography. B, Analytical technologies in the biomedical and life sciences*, 814(2), p. 251—258. doi: 10.1016/j.jchromb.2004.10.042.

[516] Corsini, E. *et al.* (2005) 'Immunomodulatory effects of the fungicide Mancozeb in agricultural workers', *Toxicology and Applied Pharmacology*. Academic Press, 208(2), pp. 178–185. doi: 10.1016/J.TAAP.2005.02.011

Table X13-9: Exposure to ETU				
Sector/use	**Country**	**Study**	**Air concentration**	**Urine**
Agricultural workers handling Maneb (EBDC pesticide)	Finland	Savolainen et al. (1999)[513]	0.004–3.3 mg/m^3 (breathing zones) 0.006–0.8 mg/m^3 (tractor cabins)	
Agricultural workers handling EBCD pesticides	Italy	Sottani et al. (2003)[514]		1.9 to 8.2 µg/L (post-exposure) vs. 0.5 to 2.1 µg/L (pre-exposure)
Agricultural workers handling EBDC pesticide	Italy	Fustinoni et al. (2005)[515]		8.5 µg/g, with a maximum of 40.1 µg/g (post-exposure) vs. <1.6 µg/g of creatinine (pre-exposure)

X13.6 Current Risk Management Measures (RMMs)

X13.6.1 Overview of RMMs, specified by REACH

As outlined above, ETU is used at industrial sites in the following processes:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 4: Chemical production where opportunity for exposure arises;
- PROC 5: Mixing or blending in batch processes;
- PROC 7: Industrial spraying;
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities;
- PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing);
- PROC 10: Roller application or brushing;
- PROC 13: Treatment of articles by dipping and pouring;
- PROC 14: Tabletting, compression, extrusion, pelletisation, granulation;
- PROC 15: Use as a laboratory reagent;
- PROC 21: Low energy manipulation of substances bound in materials and/or articles; and
- PROC 24: High (mechanical) energy work-up of substances bound in/or materials or articles

PROC codes 4–24 present a risk of exposure, so protective measures would need to be followed to reduce this exposure risk. PROCs 1 and 3 are closed systems so do not present an exposure risk.

The risk reduction measures for exposure control, as discussed in the REACH registration dossier for ETU, are described in Table X13-10.

Table X13-10: ETU REACH protective measures	
Measure	**Details**
Organisational measures	Maintain strict body hygiene; avoid contact with skin, eyes and dust inhalation
Engineering measures	None listed
Respiratory protection	Dust mask
Eye protection	Safety glasses
Hand protection	Gloves
Skin and body protection	Protective clothing
Source: ECHA (2018): Imidazolidine-2-thione REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/13536/9	

X13.6.2 Overview of RMMs from safety data sheets

The safety data sheet supplied to downstream users recommends that, where the risk assessment shows that air-purifying respirators are appropriate, they use a full-face particle respirator type P3 (EN 143) respirator cartridges, as a backup to engineering controls. If the respirator is the only means of protection, then the use of a full-face supplied air respirator is recommended.[517]

X13.6.3 Best/good practice examples

There was one consultation response from a company using ETU, but they did not mention any voluntary industry initiatives. No examples good/best practice in eliminating and/or managing occupational risks were found.

Manufacture of ETU

ETU is manufactured using a closed process and is packed in a closed system, such as a flexible container. There is some risk of exposure, caused by the scattering of ETU during packaging, but an oil component is usually added to ETU to suppress scattering. In addition, preventative measures, as stipulated by regulation, include ventilation systems and personal protective equipment, including masks, in the working environment where scattered ETU particles are expected, thereby strictly controlling and minimising the exposure of workers to ETU. The transportation and storage of ETU occurs within a closed system, minimising the risk of worker exposure.

ETU in the manufacture of rubber products

Where the manufacturers of chloroprene rubber articles use sealed-type kneading machines during the compounding process, the scattering of ETU is prevented and worker exposure is negligible. Even where chloroprene rubber articles are made using open-type kneading machines, manufacturers take precautions to prevent the scattering of ETU, in line with regulatory specifications, including appropriate ventilation and personal protective equipment, such as masks.

[517] Sigma Aldrich (2014): 2-Imidazolidinethione Safety Data Sheet. Available at: https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=I504&brand=ALDRICH&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fsearch%3Fterm%3D2-Imidazolidinethione%26interface%3DAll%26N%3D0%26mode%3Dmatch%2520partialmax%26lang%3Den%26region%3DGB%26focus%3Dproduct

In addition to implemented RMMs to ensure worker exposure to ETU is minimised in the rubber industry, a collaborative project, called SafeRubber[518] was undertaken between the years 2010 and 2013. The aim was to find 'a safer alternative replacement for thiourea accelerators in the production process of chloroprene rubber,' and was focussed on SME associations. Industrial trials showed that the candidate substitute, SRM102, is an effective replacement for ETU in both general purpose and high-quality chloroprene based compounds.

X13.6.4 Voluntary industry initiatives

There is no evidence of voluntary industry initiatives, other than the SafeRubber project mentioned above, including product stewardship and social partner agreements, to reduce exposure to ETU.

X13.7 Market analysis

X13.7.1 Number of enterprises in each sector by size

Table X13-11: Number and proportion of SMEs by size of enterprise and sector									
Sector	TOTAL	Micro		Small		Medium		Large	
	No. firms	No. firms	% of total	No. firms	% of total	No. firms	% of total	No. firms	% of total
A1.1	-	-	-	-	-	-	-	-	-
A1.2	-	-	-	-	-	-	-	-	-
A2.1	-	-	-	-	-	-	-	-	-
C20.1	**8,980**	5,190	58%	2,010	22%	980	11%	360	4%
C20.2	**630**	360	57%	140	22%	100	16%	20	3%
C22.1	**7,690**	5,090	66%	1,740	23%	640	8%	230	3%
C24	**16,460**	10,240	62%	3,640	22%	1,880	11%	690	4%
Source: Eurostat's Structural Business Statistics database									

X13.7.2 Number of estimated exposed enterprises in each sector by size

Table X13-12: Estimated number and proportion of SMEs by size of enterprise and sector									
Sector	TOTAL	Micro		Small		Medium		Large	
	No. firms	No. firms	% of total	No. firms	% of total	No. firms	% of total	No. firms	% of total
A1.1	-	-	-	-	-	-	-	-	-
A1.2	-	-	-	-	-	-	-	-	-
A2.1	-	-	-	-	-	-	-	-	-
C20.1	**898**	519	58%	201	22%	98	11%	36	4%
C20.2	**126**	72	57%	28	22%	20	16%	4	3%
C22.1	**3,461**	2,291	66%	783	23%	288	8%	104	3%
C24	-	-	-	-	-	-	-	-	-
Source: Eurostat's Structural Business Statistics database *Notes: 10% of C20.1 enterprises are assumed to have exposed workers, 20% of C20.2 enterprises, 45% of C22.1 enterprises.*									

[518] SafeRubber. The SafeRubber Project (Presentation). (2013). https://www.perainternational.com/wp-content/uploads/2014/03/SafeRubber-Dissemination-Presentation.pdf (accessed 10/08/18)

X13.7.3 Average turnover by size of enterprise

Table X13-13: Average turnover by sector and size of enterprise, 2016												
Sector	Micro			Small			Medium			Large		
	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m
A1.1	-	-	-	-	-	-	-	-	-	-	-	-
A1.2	-	-	-	-	-	-	-	-	-	-	-	-
A2.1	-	-	-	-	-	-	-	-	-	-	-	-
C20.1	6,854	5,190	1.32	19,422	2,010	9.66	68,909	980	70.32	234,358	360	650.99
C20.2	194	360	0.54	852	140	6.09	4,697	100	46.97	5,005	20	250.25
C22.1	1,569	5,090	0.31	5,271	1,740	3.03	10,533	640	16.46	59,602	230	259.14
C24	5,600	10,240	0.55	22,615	3,640	6.21	71,133	1,880	37.84	242,830	690	351.93
Source: Eurostat's Structural Business Statistics database												

X13.7.4 R&D expenditure

Table X13-14: Business expenditure on R&D per sector (in € million), EU28		
Sector	Data availability	R&D expenditure (in €m)
A1.1	A	520.3
A1.2	A	520.3
A2.1	A	520.3
C20.1	C20	6,659.7
C20.2	C20	6,659.7
C22.1	C22	2,371
C24	C24	1,361.2
Source: Eurostat *Notes: EU28 totals do not include data for some member states, due to confidentiality.*		

X13.8 Burden of ill health

X13.8.1 Effects leading to cases of ill-health

To assess the potential cases of ill health, three exposure scenarios are considered:

- Member state OEL: 0.1 mg/m^3 (Poland and Finland)
- 100 x DNEL (inhalation): 7 mg/m^3
  - Highest value from exposure data:
  - For ETU directly: 0.24 mg/m^3
  - For indirect exposure through use of EBDC pesticide: 3.3 mg/m^3

OEL exposure scenario

Table X13-15 shows that the threshold for effect does not lie below the OELs set by Finland and Poland of 0.1 mg/m^3 for any endpoint measured. If it is assumed that no workers are exposed to ETU above this OEL, then no fertility or developmental effects will occur in those working with ETU.

100x DNEL exposure scenario

One endpoint was found to have a threshold for effect that lies below 7 mg/m^3 ETU (100 x DNEL) and this is a decrease in iodine uptake – female. These are presented in Table X13-15. The decrease in iodine uptake would have an effect upon pregnant women[519] and this is used to calculate the number of cases and endpoints created.

Highest value from exposure data scenario

If the highest value from evidence of exposure to ETU for those manufacturing rubber products is used, 0.24 mg/m^3, the threshold for effect does not lie below this for any endpoints measured. If it is assumed that no workers are exposed to ETU above this level, then no fertility or developmental effects will occur in those working with ETU.

If the highest value from evidence of exposure to ETU for agricultural workers handling EBDC pesticides or manufacturers of EBDC is used, 3.3 mg/m^3, the threshold for effect does not lie below this for any endpoints measured. If it is assumed that no workers are exposed to ETU above this level, then no fertility or developmental effects will occur in those working with ETU.

Table X13-15: ETU effects based on different exposure values.

Effect	Threshold	DRR	Exposure scenario	Value
Decrease in iodine uptake	4.38 mg/m3	y=-2.99x+13.10	OEL scenario: 0.1 mg/m^3	-
			100x DNEL scenario: 7 mg/m^3	-7.8%
			EBDC exp scenario: 3.3 mg/m^3	-
			ETU exp scenario: 0.24 mg/m^3	-

Source: RPA analysis

X13.8.2 Cases of ill health

A reduction in iodine below 150 µg/g in pregnant women leads to a higher proportion of children having an IQ in the lowest quartile (below an IQ of 90). The study finds that 75% of the women already had a low iodine below 150 µg/g. Table 2 from this study shows that 29% of children of women with iodine levels below 150 µg/g had verbal IQs at the age of eight that were in the lowest IQ quartile. This compares with 20% of children of women with iodine levels above 150 µg/g. The study also finds that the impact upon IQ continues as the mother's iodine levels fall further.

Therefore, in summary, all women who already have low iodine levels, plus women whose iodine levels are brought under the 150 µg/g level by the exposure, may have their children's IQ reduced due to a reduction in iodine levels caused by exposure to ETU.

- 75% of the 46,498 exposed women are already have low iodine levels. Of the remaining 25%, a decrease in iodine uptake is assumed to bring a further 7.8% (907 women) below 150 µg/g. Thus, 35,780 women's iodine levels are already low or would become so.
- Of these women, 2.83% will have a child in a given year, or 1,013 women.

[519] Bath S, Steer C D, Golding J, Emmett J, Rayman M P, Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC), Lancet 2013; 382: 331–37

- The average IQ under a normal distribution is 100; the 25 percentile occurs at an IQ of 90.
- If 29% of children of women with iodine levels below 150 µg/g are in the lowest quartile with an IQ of below 90, then the average IQ of this group is 98 (This was obtained by calculating the standard deviation for the IQ normal distribution, based upon a value of 90 at the 25th percentile with a Z-value of -0.674, giving a standard deviation of 14.8. As a result of the change in IQs, the IQ normal distribution is shifted to lower IQ levels. The new mean is calculated from the standard deviation, the value of the IQ (90) at the 29th percentile and the Z value for the 29th percentile, which is -0.553. The new mean or new average IQ is 98.)
- If 20% of children of women with iodine levels above 150 µg/g are in the lowest quartile with an IQ of below 90, then the average IQ of this group is 102. (This uses a similar calculation to above, but the normal distribution is shifted to higher IQ levels and the value of the IQ of 90 applies at the 20th percentile, giving a new mean or new average IQ of 102.)
- The difference in average IQ between the two groups is four IQ points.
- The impact upon IQ continues as the mother's iodine levels fall and therefore all 1,013 children may have their IQ reduced.
- However, the study team does not believe that the four point drop in IQ can be assumed to affect all children in the low iodine group and assumes an average reduction for each child of two points.

Therefore, there are 1,013 cases/year, each experiencing a reduction of two IQ points as shown in the table below**Error! Reference source not found.**.

Table X13-16: ETU – number of cases arising per year from ill-health effects – worst case scenario based upon exposure of 100 x DNEL

Effect	Exposed female workers	Births per exposed female worker /year	Cases of reduced IQ (2 points)
Decrease in iodine uptake in pregnant women leading to a decrease in the IQ of their children	35,780	1,013	1,013

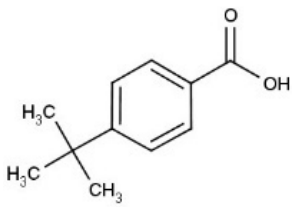
Source: RPA analysis
Notes: female workers whose iodine levels are already low are vulnerable to further reductions in their iodine levels.

Annex 14 4-tert-butylbenzoic Acid (pTBBA)

X14.1 Introduction

X14.1.1 Relevant substance(s)

4-tert-butylbenzoic acid (4-(1,1-Dimethylethyl)benzoesäure, 4-tert-Butylbenzoesaeure, acide p-(terc.) butylbenzoique, P-tert-butylbenzoic acid, pTBBA) is an organic acid mostly used as an intermediate in the production of methyl and vinyl esters of pTBBA.



p-tert-butylbenzoic acid (pTBBA); CAS number: 98-73-7; EC number: 202-696-3;
Molecular formula: $C_{11}H_{14}O_2$

The esters of pTBBA are important precursors of UV sun screens.[520] pTBBA is also an intermediate metabolite of Lysmeral/2-4-tertbutylbenzylpropinolaldehyde metabolism (The reproductive effects of 2-4-tertbutylbenzylpropinolaldehyde are in section X16.2.1.). Lysmerylic acid, formed by oxidation of Lysmeral, undergoes putative decarboxylation, followed by oxidation to the propanoic acid derivative and beta-oxidation, leading to formation of pTBBA.

X14.1.2 Hazard classification(s)

pTBBA has harmonised classification, under annex VI of regulation (EC) No 1272/2008 (CLP regulation), as Acute Tox. 4, STOT RE 1 and Repro 1B. Details of this classification, along with other notified classification and labelling, according to CLP criteria, are listed in Table X14-1.

[520] European Union Risk Assessment Report, 4-TERT-BUTYLBENZOIC ACID, FINAL APPROVED VERSION, July 2009. https://echa.europa.eu/documents/10162/15c7dba3-848b-463b-ae60-c6f187b7b5d4

Table X14-1: pTBBA - Hazard classification		
Hazard class and category code	**Hazard statement code**	**Explanation**
Harmonised classification – Annex VI of regulation (EC) No 1272/2008 (CLP regulation)		
Acute Tox. 4	H302	Harmful if swallowed
STOT RE 1	**H372**	**Causes damage to organs through prolonged or repeated exposure**
Repr. 1B	**H360F**	**May damage fertility**
Notified classification and labelling according to CLP – lead dossier of REACH registration joint submission		
Acute Tox. 4	H302	Harmful if swallowed
Repr. 1B	**H360**	**May damage fertility**
STOT RE 1	**H372 (oral)**	**Causes damage to organs through prolonged or repeated exposure (Target organs: kidney, testis)**
Acute Tox. 4	H302	Harmful if swallowed
Repr. 1B	**H360**	**May damage fertility or the unborn child**
STOT RE 1	**H372**	**Causes damage to organs through prolonged or repeated exposure (Affected organs: kidney, testis, brain, spinal cords (neuronal dysfunctions), peripheral blood)**
Aquatic chronic 2	H411	Toxic to aquatic life with long-lasting effects

X14.1.3 Existing OELs and BLVs

Existing occupational exposure limits (OELs) and biological limit values (BLVs) for pTBBA are listed in Table X14-2. Of the EU member states, an OEL could only be found for Germany, and despite harmonised classification as Acute Tox. 4, STOT RE 1 and Repr. 1B, there is no listed harmonised EU OEL. No biological limit values (BLVs) could be found for any member states or for the EU.

Table X14-2: pTBBA - summary of existing OELs and BLVs in EU countries and key non-EU countries		
Country	**OEL (mg/m^3)**	**Other**
EU Member States		
Germany	2 (inhalable fraction)	STEL: 4 mg/m^3 (inhalable fraction)
The Netherlands		SML: 0.1 mg/kg
Third countries		
China	2 (inhalable fraction, TWA)	STEL: 4 mg/m^3
Turkey	2 (inhalable aerosol)	
Source: RPA research *Notes: SML, specific migration limit; TWA, time-weighted average; STEL, short-term exposure limits*		

X14.1.4 DNEL (Derived No Effect Level)

The occupational long term DNEL for worker inhalation hazard[521] is set at 0.067 mg/m^3, based upon a NOAEC of 2.5 mg/m³ divided by the assessment/ protection factor of 37.5 rated for developmental toxicity and teratogenicity.

The occupational long term DNEL for worker dermal hazard is set at 0.017 mg/kg bw/day, including an assessment/ protection factor of 450 rated for developmental toxicity and teratogenicity.

[521] ECHA dossier for 4-tert-butylbenzoic acid. https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/12153/7/1

X14.2 Summary of health endpoints, thresholds and DRRs

X14.2.1 Relevant health endpoints

Given its CLH hazard classification, Repr. 1B H360F, pTBBA may damage fertility. Literature review was undertaken to identify all potentially relevant effects and these are shown in Table X14-3 for those effects that are relevant to human reproductive and developmental health, along with a monetised health effect that may be used to value it.

Those identified were all derived from animal studies and no human studies with relevant data were found. Relevant effects were grouped according to their effects on the reproductive system and embryonic/foetal development. A general no-effect threshold in humans was derived, along with a slope and dose-response curve.

Table X14-3: pTBBA – summary of health effects

Health effects	Fertility/development		Male/ Female exposure	Monetisable effect correlate
	Fer	Dev		
Reduction in relative testes weights[522]	Fer		M	Impaired or reduced fertility – male
Reduction in mean relative testes weight[523]	Fer		M	Impaired or reduced fertility – male
Lower testicular sperm counts[524]	Fer		M	Impaired or reduced fertility – male
Reduction in mean sperm count[523]	Fer		M	Impaired or reduced fertility – male
Infertility/inability to impregnate[525]	Fer		M	Impaired or reduced fertility – male
Source: RPA and Verisk3E analysis				

No health effects for the following groupings were found:

- Fertilisation/implantation

[522] Hunter CG, Chambers PL and Stevenson DE (1965). Studies on the oral toxicity of p-tert-butyl benzoic acid in rats. Fd. Cosmet. Toxicol. 3, 289-298 as cited in European Union Risk Assessment Report for 4-TERT-BUTYLBENZOIC ACID, FINAL APPROVED VERSION, July 2009. https://echa.europa.eu/documents/10162/15c7dba3-848b-463b-ae60-c6f187b7b5d4

[523] Lu CC, Cagen SZ, Darmer KI and Patterson DR (1987). Testicular effects induced by dermal or inhalation exposure to para-tertiary butyl benzoic acid (pTBBA) in Fischer 344 rats. J. Am.Coll. Toxicol., 6, 233-243. and Cagen SZ, Patterson DR, Wimberly HC, Lu CC and Gardiner TH (1989) Toxicity induced by subchronic dermal exposure to paratertiary butyl benzoic acid (pTBBA) in Fischer 344 rats. J.Am. Coll. Toxicol. 8,1027-1038. as cited in European Union Risk Assessment Report for 4-TERT-BUTYLBENZOIC ACID, FINAL APPROVED VERSION, July 2009. https://echa.europa.eu/documents/10162/15c7dba3-848b-463b-ae60-c6f187b7b5d4

[524] Shell (1982) Shell Development Company – Westhollow Research Center, Procol No. WTP-162, Regulatory Information Record No. WRC RIR-244, Seven day dust inhalation study in rats with para-tertiary butyl benzoic acid (pTBBA), 1982 as cited in European Union Risk Assessment Report for 4-TERT-BUTYLBENZOIC ACID, FINAL APPROVED VERSION, July 2009. https://echa.europa.eu/documents/10162/15c7dba3-848b-463b-ae60-c6f187b7b5d4

[525] Hoechst AG (1987).[Pharma Forschung Toxikologie und Pathologie (unpublished report)] p-tButylbenzoesäure-Fertilitätsversuchan männlichen Wistar-Ratten bei oraler Verabreichung. Pensler, Baeder, Weigand, Mayer und Langner, Bericht Nr. 86.1472, 11.März 1987. As cited in CLH report PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING4-tert-Butylbenzoic acid, June 2010. https://echa.europa.eu/documents/10162/13626/clh_axvirep_4_tert_butylbenzoic_acid_en.pdf

- Embryonic/foetal development
- Childbirth/lactation
- Post-natal development (until puberty)

Other than reproductive toxicity, experimental data, reported in the registration dossier, describes other maternal health effects in animal experiments. These include damage to various organs and evidence of neuronal effects, see Table X14-4.

Table X14-4: pTBBA - maternal health effects	Threshold (mg/m³)
Increase in liver weight[522]	1.05
Increase in kidney weight[522]	1.05
Necrosis of tubular and papillary cells in kidney[522]	1.05
Increase in liver weight[522]	1.40
Increase in kidney weight[522]	1.40
Fore and hind limb paralysis, hunched posture, tremors, convulsions, gait abnormalities, hypo activity, and abnormal respiration[524]	9.38
Perineal and abdominal urine staining, dehydration, white powder on the hair coat, small red thymus, bright red lungs, pinpoint red gastric foci, enlarged tan livers, reduced digesta and body fat stores[524]	9.38
Increase in absolute and relative liver weight[524]	9.38
Increase in absolute and relative kidney weight[524]	9.38
Increase in absolute and relative liver weight[526]	11.3
Incidence of body tremor[526]	11.3
Facial staining and hair loss[526]	11.3
Hypo activity[526]	11.3
Lower final body weight of males[527]	52.5
Source: RPA and Verisk3E analysis	

X14.2.2 Summary of thresholds and DRRs

Table X14-5: pTBBA - selected occupational endpoints: thresholds and dose response relationship				
Effects	**Threshold dose ((mg/ m³) (no effects)**	**Upper limit (mg/ m³)**	**Slope (%/mg/m³)**	**Monetisable effect correlate**
Reduction in relative testes weights[522]	10.5	36.8	-0.86	Impaired male fertility
Reduction in mean relative testes weight[523]	61.3	122.6	-0.67	Impaired male fertility
Lower testicular sperm counts[524]	9.38	79.38	-0.49	Impaired male fertility
Reduction in mean sperm count[523]	61.3	122.6	-1.56	Impaired male fertility

[526] HRC (1995). Huntingdon Research Centre on behalf of BG Chemie, p-t-Butylbenzoic acid (BG No. 54) – 28 day repeat dose inhalation neurotoxicity study in rats (snout only exposure), 1995 as cited in European Union Risk Assessment Report for 4-TERT-BUTYLBENZOIC ACID, FINAL APPROVED VERSION, July 2009. https://echa.europa.eu/documents/10162/15c7dba3-848b-463b-ae60-c6f187b7b5d4

[527] Shell Research Ltd. London (1975). Sittingbourne Research Centre Tunstall Laboratory. Studies on the percutaneous toxicity of para-tertiary butyl benzoic acid (pTBBA) to rats and rabbits. Unpublished report 0830/75 of October 1975 as cited in European Union Risk Assessment Report for 4-TERT-BUTYLBENZOIC ACID, FINAL APPROVED VERSION, July 2009. https://echa.europa.eu/documents/10162/15c7dba3-848b-463b-ae60-c6f187b7b5d4

Table X14-5: pTBBA - selected occupational endpoints: thresholds and dose response relationship				
Effects	**Threshold dose ((mg/ m³) (no effects)**	**Upper limit (mg/ m³)**	**Slope (%/mg/m³)**	**Monetisable effect correlate**
Infertility/inability to impregnate[525]	2.80	13.8	0.91	Impaired male fertility
Source: RPA and Verisk3E analysis				

The figures for "infertility/inability to impregnate" are taken from a study of Wistar rats[525], which focussed on male fertility. Ten males per group were fed a diet containing 0, 20, 100, or 500 ppm pTBBA, continuously for a period of 70 days before starting with mating trials. Infertility/inability to impregnate was measured by the ability of a male rat to impregnate a female rat, following two mating trials.

There is no documented evidence of an effect of pTBBA exposure on female workers and the off-spring, in terms of fertility and developmental effect.

X14.3 Relevant sectors, uses, and operations

The ECHA registration dossier lists the industrial uses of pTBBA as:[528]

- An intermediate in the manufacture of resins;
- Use in resins (containing pTBBA) as a binding agent in the manufacture of paints / coatings.

According to industry information gathered as part of the ECHA risk assessment report[529], the two main EU market suppliers have identified three uses of pTBBA. It is mainly used in the EU as a thermal stabiliser in PVC. For this purpose, it is first converted into pTBBA metal salts (Metal-p-tert-butylbenzoate, Me-pTBB). Since both pTBBA and its metal salts are present in their ionised form (as p-tert-butylbenzoate) under environmental conditions, the transformation into metal salts does not change the identity of the substance to which the environment is exposed. Consequently, the downstream use in PVC is covered by this analysis.

The second most important use of pTBBA in the EU is as process regulator (chain stop agent) in the polymers industry in the production of alkyd and polyester resins. A minor amount of pTBBA is also used as an intermediate in the chemical industry for producing esters of pTBBA.

The two main EU market suppliers of pTBBA state that open applications are not supported, i.e. applications where industrial users can come into contact with pTBBA, for example in cutting fluids for industrial use. However, different national registers list products which contain pTBBA:

For Denmark, the Nordic Product Register SPIN 1.0 lists seven products of "paints, lacquers and varnishes" using pTBBA in a quantity of 0.1 tons in 2000. Six products of these were registered under the industrial use category of "sale, maintenance and repair of motor vehicles and motorcycles".

In Norway, the most frequent use of the registered products is the use in paints and varnishes. The most frequent industrial use category in Norway is construction (SPIN further gives "manufacture of

[528] ECHA. 4-tert-butylbenzoic acid registration dossier. https://echa.europa.eu/registration-dossier/-/registered-dossier/12153/3/1/4 (accessed 6/8/18).

[529] ECHA. European Union Risk Assessment Report: 4-tert-butylebenzoic acid. https://echa.europa.eu/documents/10162/15c7dba3-848b-463b-ae60-c6f187b7b5d4 July 2009 (accessed 6/8/18)

basic metals" as a frequent category). The Norwegian Product Register contained all together seven products with a pTBBA content of 0-1 % and a total volume of 2 tons, and 19 products with a pTBBA content of 1-10 % and a total volume of 18 tons.

The Swedish Product Register (information from the year 2001) contains four pTBBA products altogether with specified uses of "corrosion inhibitors" and "raw material for synthesis". The industrial categories reported were "fabricated metal products" and "industry for other organic basic chemicals" SPIN, indicates that these categories used 27 tons in Sweden.

The Finnish Product Register did not contain any entries for pTBBA in April 2002. Of the four national Nordic Product Registers, only the Norwegian Product Register (April 2002) contained products in consumer use (no information on the use category is provided).

The Swiss Product Register (September 2002) contains the following products for professional uses: one product as corrosion inhibitor (concentration 10–50%), one product for use in paints, two products as process regulator and two products for photochemicals (concentration 1-10 %).

The sectors and uses of pTBBA are summarised in Table X14-6. Based upon the information above, the two sectors that the study team believes are the most likely to cause exposure to workers are C22 Manufacture of rubber and plastic products and C20.3 Manufacture of paints, varnishes and similar coatings, printing ink and mastics.

Table X14-6: pTBBA – sectors and uses

Sector	Uses and/or activities	Notes (NACE codes, etc.)
Manufacture of other organic basic chemicals	Production	C20.1.4
Manufacture of other organic basic chemicals	Use as an intermediate for producing esters	C20.1.4
Manufacture of rubber and plastic products	Used for the manufacture of thermal stabilisers in PVC; Used as a process regulator in polymer manufacturing	C22
Manufacture of paints, varnishes and similar coatings, printing ink and mastics	Use as a modifier in resins (processing)	C20.3
Wholesale and retail trade and repair of motor vehicles and motorcycles	Paints, lacquers and varnishes	G45
Construction Painting and glazing	Paints, lacquers and varnishes	F F43.3.4
Manufacture of basic metals	Corrosion inhibitors	C24
Manufacture of fabricated metal products, except machinery and equipment	Corrosion inhibitors	C25

Source: ECHA risk assessment report[528]

X14.3.1 Production

Production of pTBBA in the EU ended in 2006, therefore this activity does not need to be considered in the analysis[528].

X14.3.2 Use as an intermediate

pTBBA is only used at one site as an intermediate and emissions from this site are negligible[528]. The use of pTBBA for this purpose is excluded from this analysis.

X14.3.3 Use as a stabiliser in PVC (production of pTBBA metal salts)

During the manufacture of liquid mixed metal stabilisers, pTBBA is converted into its metal salts. The process starts with the mixing of salts of different acids to produce a one pot reaction. Then, in a closed system, organic acids, including pTBBA, are reacted with mixed metal oxides or hydroxides in a non-aqueous medium. A small amount of process water arises from the salification reactions and is removed from the mixture by distillation. It only contains small amounts of pTBBA and is treated before disposal. It is either discharged to the sewer in agreement with local authorities or incinerated. Finally, other additives are added to the mixture. These processes occur in the chemical industry and the liquid stabiliser preparation produced is supplied to the PVC industry[528].

X14.3.4 Use as a stabiliser in PVC (compounding and conversion)

According to the European Stabiliser Producers Association (ESPA), the next two life-cycles stages (compounding and conversion) occur generally at one site. The mixed metal stabilisers are used entirely in the processing of plasticised PVC. Liquid metal stabilisers are used in both major compounding methods and their subsequent conversion methods[530]. The major use of stabilizers is in dry blending and calendering operations. Other uses are injection moulding, such as for footwear, and extruded tubing, such as for garden hoses, which are made by dry blending. The main use of plastisol is for flooring which is made by spread coating. The highest emission factors for a plastics processing site are for dry blending followed by calendering[531].

X14.3.5 Use as a stabiliser in PVC (service life)

During the heat stabilising process of PVC, metal ions bind with chloride escaping from the polymer due to thermal deterioration. p-tert-Butyl ion is expected to be unchanged during this process in the polymer matrix. Therefore, there will be releases during its service life.

X14.3.6 Use as a modifier in resins (processing)

The use of pTBBA as a chain stop agent in resins improves the resin's properties, such as its drying behaviour, hardness and solvent resistance. During the polymerisation phase of resin production, pTBBA is added and reacts covalently with the usual alkyd monomers[532], which makes this an intermediate use. According to industry, pTBBA is added to the precursors' mix in the proportion of 1–10 % w/w, but unreacted pTBBA is left in very low concentrations (< 0.1 % w/w). Therefore, downstream uses of resins are not considered further in this study.

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[530] ESPA Release Measurement for PTBBA during Metal salt production. Process descriptions for Production of PTBBA Metal salts and Use as Additive in PVC. Update 6.7.2006. European Stabiliser Producers Association, Brussels.

[531] OECD Series on Emission Scenario Documents Number 3, Emission Scenario Documents on Plastics Additives ENV/JM/MONO/2004(8), June 2004.

[532] Jones, F.N. Alkyd Resins. In: Ullmann's Encyclopedia of Industrial Chemistry, Online Posting Date January 15, 2003. John Wiley & Sons, Inc.

Table X14-7: pTBBA - use descriptors for identified uses	
Area	**Process category (PROC)**
Use as intermediate in the manufacture of resins (industrial)	
PC19: Intermediate PC32: Polymer preparation and compounds	PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 6: Calendering operations PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 14: Production of preparations or articles by tabletting, compression, extrusion, palletisation PROC 15: Use as laboratory reagent
Use of resins (containing pTBBA) as binding agent in manufacture of paints/coatings (industrial)	
PC9a: Coatings and paints, thinners, pain removers	PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 15: Use as laboratory reagent
Source: pTBBA registration dossier[528]	

X14.4 Exposed workforce

No information about exposed workforces was found in the SUMER[533], GESTIS[534] or ASA[535] databases for this substance.

X14.4.1 Total number of exposed workers

The estimated number of exposed workers in the two sectors is shown intable X14-8.

Table X14-8: pTBBA – estimated exposed workforce by sector – women of reproductive age (15–49)		
Sector	**Assumptions**	**Estimated no. of exposed workers of reproductive age**
C22 Manufacture of rubber and plastic products – used as a thermal stabiliser in PVC	• 1,232,400 men of reproductive age working in the manufacture of rubber and plastic (C22) • 40% of enterprises are using pTBBA	98,592

[533] France: Working conditions and occupational risks: SUMER 2010 https://www.eurofound.europa.eu/publications/article/2013/france-working-conditions-and-occupational-risks-sumer-2010

[534] IFA Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (2017): GESTIS - Internationale Grenzwerte für chemische Substanzen. Available at: http://www.dguv.de/ifa/GESTIS/GESTIS-Internationale-Grenzwerte-für-chemische-Substanzen-limit-values-for-chemical-agents/index.jsp

[535] ASA Finland Institute of Occupational Health (2014): Those who cause cancer substances and methods in their profession exposed in Finland. Available at: https://www.julkari.fi/handle/10024/131073

Table X14-8: pTBBA – estimated exposed workforce by sector – women of reproductive age (15–49)		
Sector	**Assumptions**	**Estimated no. of exposed workers of reproductive age**
and process regulator in polymer manufacture	• 20% of workers in enterprises using pTBBA are potentially exposed to it (working in processes related to pTBBA)	
C20.3 Manufacture of paints, varnishes and similar coatings, printing ink and mastics	• 936,400 women of reproductive age working in manufacture of chemicals and chemical products • 13.2% of C20 enterprises are C20.3 • 50% enterprises are using pTBBA • 20% of workers exposed to pTBBA manufacturing process	12,360
TOTAL		**110,952**
Sources: Eurostat, RPA analysis		

X14.5 Exposure levels

X14.5.1 Exposure routes

The possible routes of exposure are inhalation and dermal.[536]

X14.5.2 Current exposure levels

Two occupational exposure scenarios have been considered[520]:

1. Production and further processing of pTBBA
2. Production of alkyd resins in the polymers industry.

Air concentrations of pTBBA in different pTBBA salt producing plants were measured in the range of 0.01 (for normal situation) to 0.05 mg/m^3 (for worst case scenario). Workplace air concentrations of pTNBA for a pTBBA-ester production plant were reported as ranging up to 1.31 mg/m^3.

Additionally, daily inhalation exposure to an 8 hr time weighed average concentration (8 hr TWA) of 0.0625 mg/m^3 (EASE estimation[537]) were considered to represent a reasonable worst case situation.

Occupational exposures to pTBBA were investigated in a cohort of 90 male volunteers of a pTBBA producing facility.[538] The control group consisted of 103 volunteers who did not work in the facility and who had not been exposed to any known testicular toxin. Air concentrations at the workplace among operators and drummers ranged from less than 0.1 mg/m^3 to 0.5 mg/m^3. Eight individuals in the study group (15.7 %) had sperm counts of less than 20 million sperm/ml (e.g. in the sub-fertile

[536] Sigma Aldrich (2017): 4-tert-butylbenzoic acid Safety Data Sheet. Available at: https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=150355&brand=ALDRICH&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2F150355%3Flang%3Den .

[537] Estimation and Assessment of Substance Exposure Physico-chemical properties (EASE) is a general model that may be used to predict workplace exposure to a wide range of substances hazardous to health. Evaluation and Further Development of EASE Model 2.0

[538] Whorton MD, Stubbs HA, Obrinsky A Testicular function of men occupationally exposed to para-tertiary butyl benzoic acid Scand J Work Environ Health 1981;7(3):204-213 http://www.sjweh.fi/download.php?abstract_id=3113&file_nro=1

range), compared to 7 subjects in the control group. This difference was not statistically significant and had no clinically detectable effect on testicular function and possible pTBBA-associated infertility of the workers.

All data available are for air concentrations; no records of urine or serum concentrations were found.

Table X14-9: pTBBA - Exposure concentrations from studies			
Sector/use	**Country**	**Study**	**Air concentration mg/m3**
Salt producing plants	Not stated	EU Risk Assessment[539]	0.01–0.05
pTBBA-ester production plant	Not stated	EU Risk Assessment	Up to 1.31
pTBBA producing facility – operators and drummers	USA	Whorton et al. (1981)[538]	0.1–0.5

X14.6 Current Risk Management Measures (RMMs)

X14.6.1 Overview of RMMs, specified by REACH

As outlined above, pTBBA is used at industrial sites in the following processes:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 6: Calendering operations;
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities;
- PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing);
- PROC 14: Tabletting, compression, extrusion, pelletisation, granulation;
- PROC 15: Use as a laboratory reagent; and

PROCs 2, and 6–15 present a risk of exposure, so reduction measures (such as those listed) would need to be followed. PROCs 1 and 3 are closed systems so do not present an exposure risk.

The risk reduction measures for exposure control, as discussed in the REACH registration dossier for pTBBA, are described in Table X14-10.

[539] European Union Risk Assessment Report, 4-TERT-BUTYLBENZOIC ACID, FINAL APPROVED VERSION, July 2009. https://echa.europa.eu/documents/10162/15c7dba3-848b-463b-ae60-c6f187b7b5d4

Table X14-10: pTBBA - REACH protective measures	
Measure	**Details**
Organisational measures	Keep away from foodstuffs, beverages and feed; avoid contact with skin; wash hands before breaks and at the end of work; vacuum clean contaminated clothing; remove soiled and contaminated clothing immediately; ensure washing facilities are available at the workplace; provide an eye bath
Engineering measures	Ensure good ventilation/exhaustion at the workplace
Respiratory protection	Use a respiratory filter device for brief exposure or low pollution; Use a respiratory protective device which is independent of circulating air for longer or intensive exposure; Short term filter device: P3 filter; Only use breathing equipment for handling the residual risk where all other risk minimising measures have been carried out, such as local exhaust and/or retention
Eye protection	Goggles recommended during refilling
Hand protection	Chemical resistant gloves; apply skin-cleaning agents and skin cosmetics after use of gloves; for using undissolved solid substance nitrile rubber (NBR), butyl rubber (BR), Polychloroprene rubber (CR) or fluorocarbon rubber (FKM) may be suitable
Skin and body protection	Protective clothing (apron, boots)
Source: ECHA (2018): 4-tert-butylbenzoic acid REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/12153/9	

X14.6.2 Overview of RMMs from safety data sheets

The safety data sheet for pTBBA recommends the following measures:[540]

- Eye/face protection: Use face shield and safety glasses that meet NIOSH (US) or EN 166 (EU) standards;
- Skin protection: Use nitrile rubber gloves for full contact and splash contact;
- Body protection: Use complete suit protection; and
- Respiratory protection: Where the risk assessment shows respiratory protection is required, then a full-face respirator type N99 (US) or type P2 (EN 143) respiratory cartridges as back up to engineering controls. If no engineering controls are used, then a full-face respirator is recommended; and
- Provide appropriate ventilation where dust can occur.

X14.6.3 Best/good practice examples

There were no consultation responses from companies using pTBBA, so we therefore have no examples of good/best practice in eliminating and/or managing occupational risks to reproductive health.

[540] Sigma Aldrich (2017): 4-tert-butylbenzoic acid Safety Data Sheet. Available at: https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=150355&brand=ALDRICH&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2F150355%3Flang%3Den

X14.6.4 Voluntary industry initiatives

There is no evidence of voluntary industry initiatives, including product stewardship and social partner agreements, to reduce exposure to pTBBA.

X14.7 Market analysis

X14.7.1 Number of enterprises and exposed enterprises in each sector

The total number of enterprises in each sector is given in Table X14-11, together with the estimated number of 'potentially exposed' enterprises based upon 40% of all enterprises in the C22 rubber and plastic industry being exposed to pTBBA and 5% of all enterprises in the C20.3 paints, varnishes and coatings industry being exposed to pTBBA.

Table X14-11: pTBBA –number of enterprises and estimated exposed enterprises split by size for 2015			
Sector	**No of enterprises**	**Estimated no of exposed enterprises (1)**	**Percentage**
C22 Manufacture of rubber and plastic products – used as a thermal stabiliser in PVC and process regulator in polymer manufacture Total	123,858	49,543	100%
Micro	81,303	32,521	66%
Small	29,364	11,746	24%
Medium	11,136	4,454	9%
Large	2,043	817	2%
C20.3 Manufacture of paints, varnishes and similar coatings, printing ink and mastics Total	7,915	3,958	100%
Micro	4,663	2,332	59%
Small	2,144	1,072	27%
Medium	864	432	11%
Large	236	118	3%
Source: Eurostat and RPA analysis *Notes: 1 50% of C20.3 enterprises and 40% of C22 enterprises are assumed to have exposed workers*			

According to the ECHA risk assessment report[520], approximately 80% of the EU's annual market volume of pTBBA is used by about 30 customers.

X14.7.2 Average turnover by size of enterprise

Table X14-12: Average turnover by sector and size of enterprise, 2016												
Sector	**Micro**			**Small**			**Medium**			**Large**		
	Turnover /€m	**No. firms**	**Ave. turnover/ €m**	**Turnover /€m**	**No. firms**	**Ave. turnover/ €m**	**Turnover /€m**	**No. firms**	**Ave. turnover/ €m**	**Turnover /€m**	**No. firms**	**Ave. turnover/ €m**
C20.3	1,138	2,280	0.50	5,176	1,080	4.79	13,846	430	32.20	20,843	120	173.69
C22	13,300	40,470	0.33	51,000	14,810	3.44	108,995	5,600	19.46	133,618	1,030	129.73

Table X14-12: Average turnover by sector and size of enterprise, 2016												
Sector	Micro			Small			Medium			Large		
	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m
Source: Eurostat's Structural Business Statistics database												

X14.7.3 R&D expenditure

Table X14-13: Business expenditure on R&D per sector (in € million), EU28		
Sector	Data availability	R&D expenditure (in €m)
C20.3	C20	6,659.7
C22	C22	2,371
Source: Eurostat *Notes: EU28 totals do not include data for some member states, due to confidentiality.*		

X14.8 Burden of ill health

X14.8.1 Cases of ill health

To assess the potential cases of ill health, three exposure scenarios are considered and detailed in Table X14-14:

- Member state OEL: 2.0 mg/m^3 (Germany)
- 100 x DNEL (inhalation): 6.7 mg/m^3
- Highest value from exposure data: 1.31 mg/m^3

OEL exposure scenario

Table X14-14 shows that the threshold for effect does not lie below the OELs set by Germany of 2.0 mg/m^3 for any endpoint measured. If it is assumed that no workers are exposed to pTBBA above this OEL, then no effects on fertility will occur in those working with pTBBA.

100x DNEL exposure scenario

One endpoint was found to have a threshold for effect that lies below 6.7 mg/m^3 pTBBA (100 x DNEL). This was 'infertility/inability to impregnate' and is presented in Table X14-14.

Highest value from exposure data scenario

If the highest value from evidence of occupational exposure to pTBBA is used, 1.31 mg/m^3, the threshold for effect does not lie below this for any endpoints measured. If it is assumed that no workers are exposed to pTBBA above this level, then no effects on fertility will occur in those working with pTBBA.

Table X14-14: pTBBA - effects based on different exposure values.				
Effect	Threshold	DRR	Exposure scenario	Value
Infertility / inability to impregnate	2.8 mg/m^3	y=0.91x-2.548	OEL scenario: 2.0 mg/m^3	-
			100x DNEL scenario: 6.7 mg/m^3	3.5%

Table X14-14: pTBBA - effects based on different exposure values.				
Effect	**Threshold**	**DRR**	**Exposure scenario**	**Value**
			pTBBA exp scenario: 1.31 mg/m^3	-

X14.8.2 Cases of ill health

In conclusion, if we assume the scenario that all 98,592 male workers exposed to pTBBA are exposed at a level 100x DNEL (6.7 mg/m^3) and the prevalence of male infertility is 2%, or that 1,972 workers will be infertile. The DRR indicates that number of infertile men will increase by 3.5% or that 69 cases will be caused by this exposure, see Table X14-15.

Table X14-15: pTBBA – number of cases arising per year from ill-health effects – worst case scenario based upon exposure of 100 x DNEL			
Effect	**Exposed male workers**	**No of infertile exposed males**	**Cases**
Infertility / inability to impregnate	98,592	1,972	69
Source: RPA analysis *Notes: female workers whose iodine levels are already low are vulnerable to further reductions in their iodine levels.*			

Annex 15 2-Ethoxyethanol

X15.1 Introduction

X15.1.1 Relevant substance(s)

2-ethoxyethanol (EC No: 203-804-1; CAS No: 110-80-5) is a monoglycol ether with linear structure $C_2H_5OCH_2CH_2OH$. Other names for the compound include ethylene glycol monoethyl ether and ethylene glycol ethyl ether. Consistent with common abbreviations for other monoglycol ethers, in the present report we refer to 2-ethoxyethanol as EGEE. EGEE acetate (EGEEA) is the ester of EGEE and acetic acid.

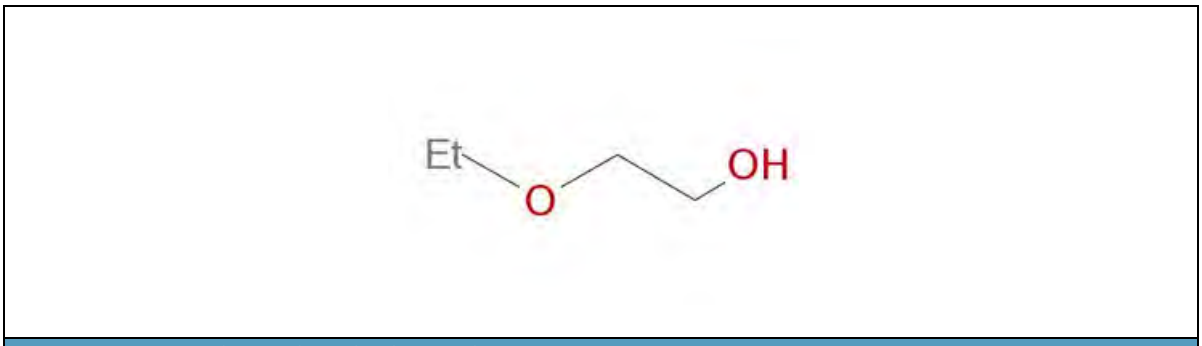


Figure X15-1: 2-ethoxyethanol - chemical structure
https://echa.europa.eu/registration-dossier/-/registered-dossier/14915/1

X15.1.2 Hazard classification(s)

2-Ethoxyethanol is listed in the CLP with the following hazard classifications[541]:

Harmonised Classification

- Repr. 1B: H360FD - May damage fertility. May damage the unborn child
- Flam. Liq. 3: H226 – Flammable liquid and vapour
- Acute Tox. 4: H302 – Harmful if swallowed
- Acute Tox. 3: H331 – Toxic if inhaled

Notified Classification

Additional notified hazard classifications include:

- Acute Tox. 4: H312 – Harmful if in contact with skin, H332 – Harmful if inhaled,
- Eye Irrit. 2: H319 – Causes serious eye irritation

In addition, the evidence that 2-Ethoxyethanol is "toxic to reproduction – breastfed babies" is considered conclusive but not sufficient for classification by the EU[542].

[541] https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/36506
[542] European Chemicals Agency (ECHA). 2018. Information on Registered Substances; Classification & Labelling & PBT Assessment; DSD – DPD. https://echa.europa.eu/registration-dossier/-/registered-dossier/14915/2/2

X15.1.3 Existing OELs and BLVs

OELs

2-Ethoxyethanol has an EU indicative OEL of 8 mg/m^3 (2ppm) for 8 hour TWA under CAD[543]. Individual Member States have introduced their own OELs and these are presented in Table X15-1 below.

Table X15-1: OELs for 2-Ethoxyethanol	
Member State	**National OEL(mg/m^3)**
Austria	8
Belgium	8
Germany	7.6, 7.5 (inhalable aerosol)
Denmark	18.5
Spain	8
Finland	7.5
France	8
Hungary	19
Ireland	8
Italy	8
Latvia	10
Netherlands	8
Poland	8
Romania	8
Sweden	8
United Kingdom	8

OEL values identified in other countries include:

- 18mg/m^3 – Australia, Israel, Japan, New Zealand, Singapore, South Korea
- 8mg/m^3 – Turkey
- 7.5mg/m^3 - Switzerland

BLVs

2-Ethoxyethanol was adopted in the List of BLVs and BGVs recommended by SCOEL in August 2007, with a BLV of 50mg 2-ethoxyacetic acid/l urine. The table below indicates BLVs adopted at Member State level.

Table X15-2: BLVs for 2-Ethoxyethanol		
Member State	**National BLV**	**Source**
Croatia	Ethoxyacetic acid in urine: 50 mg/l (at the end of the work shift)	Ministry of Economy, Labour and Entrepreneurship (Croatia) (2009)
Germany	50 mg/l ethoxyacetic acid in urine, for long-term exposure, after several shifts	BAuA (2015)
Poland	2-ethoxyethanol in urine: 60 mg/g creatinine	Survey response*

[543] Directive 2009/161/EU of 17 December 2009

Table X15-2: BLVs for 2-Ethoxyethanol		
Member State	**National BLV**	**Source**
Slovakia	50 mg/l ethoxyacetic acid in urine at end of exposure or end of work shift; after several job changes	Slovak Government Order No. 356/2015
Slovenia	Ethoxyacetic acid in urine: 50 mg/l (at the end of the work shift)	PIS (2002)
Spain	2-Ethoxyacetic acid in urine: 50 mg/l at the end of the working week	INSHT 2018 (current document), and 2019 (draft document approved on 12 December 2018
*Survey response: From consultation under "Second study to collect updated information for a limited number of chemical agents with a view to analyse the health, socio-economic and environmental impacts in connection with possible amendments of Directive 2004/37/EC, (Ref: VC/2016/0364), Final Report, RPA 2017"		

The DNELs (Derived No Effect Levels)[544] for occupational exposure to 2-ethoxyethanol are as follows:

- Long-term exposure via inhalation route – 0.083mg/m^3
- Long-term exposure via dermal route – 0.3mg/kg/day

X15.1.4 Legislation other than CAD

Pursuant to Article 59 (8) of REACH, 2-Ethoxyethanol was identified as a Substance of Very High concern (SVHC) and included in the Candidate List for authorisation in Annex XIV on 15 December 2010.

2-Ethoxyethanol is classified and labelled according to Annex VI of Reg. (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures due to its reproductive toxicity.

2-Ethoxyethanol releases are controlled through the UK Pollution, Prevention and Control (PPC) Regulations. The Scottish Environment Protection Agency[545] notes that it is also regulated through European Directives which evaluate and control the risks of substances known to be in the environment (793/93/EC) and the Solvents Directive (99/13/EC) and at an international level, 2-Ethoxyethanol is regulated through the UN/ECE Convention on Long-Range Transboundary Air Pollution and the Basel Convention concerning the transboundary movement and disposal of hazardous wastes.

X15.2 Summary of health endpoints, thresholds & DRRs

X15.2.1 Relevant health endpoints

Relevant reproductive health endpoints

The reproductive effects of exposure to 2-ethoxyethanol identified through literature review are summarised below. The table below only lists adverse effects which have been deemed as potentially relevant to humans (i.e. they have a potential for human effects correlation), a no-effect threshold

[544] https://echa.europa.eu/registration-dossier/-/registered-dossier/14915/7/1
[545] http://apps.sepa.org.uk/spripa/pages/substanceinformation.aspx?pid=49

and a Dose-Response Relationship (DRR) could be derived and the source of the data is not a study that is clearly irrelevant to occupational exposure.

Table X15-3: 2-Ethoxyethanol (EGEE) – summary of health effects			
Health effect identified in literature	Fertility/ development?		Monetisable effect correlate
	Fer	Dev	
Decreased sperm motility	Fer		Impaired fertility – male
Increased abnormal sperm	Fer		Impaired fertility – male
Decreased fertility index	Fer		Impaired fertility – male
Decreased relative right testes weight	Fer		Impaired fertility – male
Decrease in sperm concentration	Fer		Impaired fertility – male
Increase in oestrous cycle length in females	Fer		Impaired fertility – male
Decrease in relative epididymis weight	Fer		Impaired fertility – male
Decrease in spermatid count	Fer		Impaired fertility – male
Decrease in spermatid head count	Fer		Impaired fertility – male
Motility and progressiveness of sperm	Fer		Impaired fertility – male
Decreased number of live foetuses	Fer		Impaired fertility – male Impaired fertility – female
Increased pre-implantation loss	Fer		Impaired fertility – female
Decreased litters per fertile pair	Fer		Impaired fertility – female
Decreased live pups per litter	Fer		Impaired fertility – female
Decreased Proportion of pups born alive	Fer		Spontaneous abortion/still-birth
Decreased Live pup weight		Dev	No monetisable effect correlate
Decreased live foetuses per litter	Fer		Impaired fertility – male Impaired fertility – female
Increased resorptions per litter	Fer		Impaired fertility – female
Increased mean resorptions per litter	Fer		Impaired fertility – female
Increased renal pelvic dilation		Dev	Renal abnormalities - offspring
Increased no. of foetuses with limb malrotation		Dev	Skeletal abnormalities of the limbs
Increased % of foetuses with minor external and visceral defects		Dev	No monetisable effect correlate
Increased % of foetuses with minor skeletal defects		Dev	No monetisable effect correlate
Increased skeletal minor defects		Dev	No monetisable effect correlate
Increased cardiovascular defects		Dev	Cardiovascular abnormalities
Renal changes (minor anomalies)		Dev	Renal abnormalities - offspring
Ventral wall defects (major malformation)		Dev	No monetisable effect correlate
Fused aorta and pulmonary artery (major malformation)		Dev	No monetisable effect correlate
Increased foetuses with extra ribs		Dev	No monetisable effect correlate
Increased foetuses with vertebral variations		Dev	No monetisable effect correlate
Increased foetuses with sternebral variations		Dev	No monetisable effect correlate
Rib dysmorphology		Dev	No monetisable effect correlate
Supernumerary ribs per litter		Dev	No monetisable effect correlate
Increased incidences of reduced ossification per litter		Dev	No monetisable effect correlate
Cardiovascular malformation		Dev	Cardiovascular abnormalities
Renal malformation		Dev	Renal abnormalities - offspring

Table X15-3: 2-Ethoxyethanol (EGEE) – summary of health effects			
Health effect identified in literature	Fertility/ development?		Monetisable effect correlate
	Fer	Dev	
Brain malformation		Dev	No monetisable effect correlate

Table X15-4: 2-Ethoxyethanol acetate (EGEEA) – summary of health effects			
Health effect identified in literature	Fertility/ development?		
	Fer	Dev	Monetisable effect correlate
Increased post-implantation loss	Fer		Impaired fertility – female
Decreased mean no. of live foetuses	Fer		Impaired fertility – male Impaired fertility – female
Decreased mean total litter weight		Dev	No monetisable effect correlate
Increase in the rates of any skeletal defects		Dev	Skeletal abnormalities of the limbs
Increase in the rates of external and visceral minor defects		Dev	No monetisable effect correlate
Decrease in foetal weight		Dev	No monetisable effect correlate
Cardiovascular malformations		Dev	Cardiovascular abnormalities

Other health endpoints

The Draft EU Risk Assessment Report[546] published in 2008 summarised study results of repeated exposure to 2-ethoxyethanol in experimental animals, identifying potential other health endpoints. Of these, adverse effects in the haematopoietic system in both males and females, as well as a number of other adverse effects in a number of organs:

- kidneys
- tubular degeneration
- adrenal gland hypertrophy
- thymus atrophy
- liver cell degeneration

However, it was noted that these effects were considered of lower significance because of the fact that in the experiments carried out, doses where they occurred were relatively high and their occurrences were inconsistent across studies or the identified changes were not indicated as being severe.

The hazard classifications identified previously above indicate also that the substance is harmful if swallowed, toxic if inhaled, potentially harmful if in contact with skin and can cause serious eye irritation.

X15.2.2 Summary of thresholds and DRRs

The no effect thresholds (inhalation 8-hr TWA mg/m3) and effect slopes, together with the maximum air exposure concentrations (8-hr TWA mg/m3) for which the effect slopes are valid, are summarised below.

[546] European Union Risk Assessment Report - 2-Ethoxyethanol, Human Health only. Draft of October 2008, accessed at: https://echa.europa.eu/documents/10162/8df7f6fd-9268-4d0a-a881-f4cad9bb6df0

Table X15-5: 2-Ethoxyethanol (EGEE) – effects, thresholds and DRRs				
Health effect	**Threshold (mg/m^3)**	**Slope (% effect change/ mg/m^3)**	**Maximum range of slope applicability (mg/m^3)**	**Monetisable effect correlate**
Decreased sperm motility	1500	-0.03	2600	Impaired fertility – male
Increased abnormal sperm	150	0.11	1500	Impaired fertility – male
Decreased fertility index	1500	-0.08	2600	Impaired fertility – male
Decreased relative right testes weight	1575	-0.02	2625	Impaired fertility – male
Decrease in sperm concentration	191	-0.08	359	Impaired fertility – male
Increase in oestrous cycle length in females	722	0.02	1304	Impaired fertility – male
Decrease in relative epididymis weight	971	-0.05	2003	Impaired fertility – male
Decrease in spermatid count	2003	-0.01	5123	Impaired fertility – male
Decrease in spermatid head count	2003	-0.01	5123	Impaired fertility – male
Motility and progressiveness of sperm	525	0.06	1050	Impaired fertility – male
Decreased number of live foetuses	3	-0.49	30	Impaired fertility – male Impaired fertility – female
Increased pre-implantation loss	29.7	-0.10	148.7	Impaired fertility – female
Decreased litters per fertile pair	800	-0.05	1500	Impaired fertility – female
Decreased Live pups per litter	800	-0.10	1500	Impaired fertility – female
Decreased Proportion of pups born alive	800	-0.07	1500	Spontaneous abortion/still-birth
Decreased Live pup weight	800	-0.004	1500	No monetisable effect correlate
Decreased live foetuses per litter	55.44	-0.04	554.44	Impaired fertility – male Impaired fertility – female
Increased resorptions per litter	55.44	1.14	554.44	Impaired fertility – female
Increased mean resorptions per litter	700	0.56	2658	Impaired fertility – female
Increased renal pelvic dilation	148	0.01	742	Renal abnormalities - offspring
Increased no. of foetuses with limb malrotation	3	0.13	30	Skeletal abnormalities of the limbs
Increased % of foetuses with minor external and visceral defects	148	0.01	742	No monetisable effect correlate
Increased % of foetuses with minor skeletal defects	148	0.09	742	No monetisable effect correlate

Table X15-5: 2-Ethoxyethanol (EGEE) – effects, thresholds and DRRs				
Health effect	**Threshold (mg/m^3)**	**Slope (% effect change/ mg/m^3)**	**Maximum range of slope applicability (mg/m^3)**	**Monetisable effect correlate**
Increased skeletal minor defects	148	0.08	519	No monetisable effect correlate
Increased cardiovascular defects	70	0.02	700	Cardiovascular abnormalities
Renal changes (minor anomalies)	55.44	0.04	554.44	Renal abnormalities - offspring
Ventral wall defects (major malformation)	55.44	0.03	554.44	No monetisable effect correlate
Fused aorta and pulmonary artery (major malformation)	55.44	0.04	554.44	No monetisable effect correlate
Increased foetuses with extra ribs	55.44	0.10	554.44	No monetisable effect correlate
Increased foetuses with vertebral variations	55.44	0.09	554.44	No monetisable effect correlate
Increased foetuses with sternebral variations	55.44	0.06	554.44	No monetisable effect correlate
Rib dysmorphology	70	0.03	700	No monetisable effect correlate
Supernumerary ribs per litter	70	0.10	700	No monetisable effect correlate
Increased incidences of reduced ossification per litter	70	0.12	700	No monetisable effect correlate
Cardiovascular malformation	41	0.07	410	Cardiovascular abnormalities
Renal malformation	41	0.06	410	Renal abnormalities - offspring
Brain malformation	41	0.03	410	No monetisable effect correlate

Table X15-6: 2-Ethoxyethanol (EGEEA) – effects, thresholds and DRRs				
Health effect	**Threshold (mg/m^3)**	**Slope (% effect change/ mg/m^3)**	**Maximum range of slope applicability (mg/m^3)**	**Monetisable effect correlate**
Increased post-implantation loss	436	0.01	1746	Impaired fertility – female
Decreased mean no. of live foetuses	436	-0.03	1746	Impaired fertility – male Impaired fertility – female
Decreased mean total litter weight	436	-0.02	1746	No monetisable effect correlate
Increase in the rates of any skeletal defects	109	0.05	436	Skeletal abnormalities of the limbs
Increase in the rates of external and visceral minor defects	436	0.02	1746	No monetisable effect correlate

Table X15-6: 2-Ethoxyethanol (EGEEA) – effects, thresholds and DRRs				
Health effect	**Threshold (mg/m^3)**	**Slope (% effect change/ mg/m^3)**	**Maximum range of slope applicability (mg/m^3)**	**Monetisable effect correlate**
Decrease in foetal weight	109	-0.04	436	No monetisable effect correlate
Cardiovascular malformations	41	0.09	410	Cardiovascular abnormalities

X15.3 Relevant sectors, uses, and operations

X15.3.1 Overview of the relevant sectors, uses, and operations/activities

This section provides an overview of the relevant sectors, uses and activities in which occupational exposure to 2-Ethoxyethanol could potentially have occurred in the past and presently.

Table X15-7: Sectors where 2-ethoxyethanol is/has been used			
2-ethoxyethanol	Used in scientific research and development; used in laboratory chemicals; used as a solvent (used in varnish removers, lacquers, to dissolve printing inks and in the semiconductor industry)	C18.1: Printing and service activities related to printing C20: Manufacture of chemicals and chemical products C20.3: Manufacture of paints, varnishes and similar coatings, printing inks and mastics C20.4: Manufacture of soaps and detergents, cleaning and polishing preparations, perfumes and toilet preparations C26.11: Manufacture of electronic components and boards M72: Scientific research and development	https://echa.europa.eu/substance-information/-/substanceinfo/100.003.459 http://apps.sepa.org.uk/spripa/pages/substanceinformation.aspx?pid=49

The Draft EU Risk Assessment Report[547] published in 2008 indicated that due to the identified risks of the substance, 2-Ethoxyethanol had been replaced by other substances in many applications in Germany, with producers engaging in a voluntary programme to control its use in a range of applications:

- consumer goods / household products
- cosmetics
- pesticide formulations
- pharmaceutical preparations and medicines
- photo-resist mixtures for semi-conductor fabrication

[547] European Union Risk Assessment Report - 2-Ethoxyethanol, Human Health only. Draft of October 2008, accessed at: https://echa.europa.eu/documents/10162/8df7f6fd-9268-4d0a-a881-f4cad9bb6df0

- applications where exposure is poorly controlled.

The report noted that the European Technical Committee on printing inks excluded 2-ethoxyethanol from the production and distribution of printing inks and industry confirmed that it was no longer used in this application.

It was noted that the main proportion of 2-ethoxyethanol is processed to intermediates such as the 2-ethoxyethanol tert. butyl ether in the chemical industry, with the remainder used industrially as a solvent. The risk assessment noted that there was no indication that new consumer products containing 2-ethoxyethanol had been placed on the market since 1993.

The assessment noted that 2-ethoxyethanol was initially chosen for risk assessment due to its previous high production volumes and as it was widely used in open systems, such as paints for private use, surface treatment of metals and in repair industry. Besides the industrial use as intermediate and solvent, 2-ethoxyethanol was used for the formulation of paints, lacquers, varnishes and printing inks.

Based on the latest information at the time of the risk assessment report, (INEOS 2006), there is no remaining wide dispersive use of 2-ethoxyethanol outside the chemical industry. The current use pattern at the time was as follows:

- processed to intermediates in the chemical industry: 80%
- solvent use in the chemical industry: 20 %

The risk assessment report observed a significant reduction in the production of 2-ethoxyethanol between 2002 and 2006, falling from 520 tonnes in 2005 to 100 tonnes in 2006 and consequently, the assessment only considered production and use of 2-ethoxyethanol as a chemical intermediate.

A paper by the Health Council of the Netherlands[548] in 2008 indicated the following industrial activities were associated with the use of glycol ethers more generally:

- painters;
- printers;
- automobile,
- aeronautical,
- naval,
- furniture,
- building,
- textiles and dying,
- packaging and transformation,
- hair dressers and perfume,
- metal, and agricultural industry workers;
- printed circuit manufacturers;
- producers of metallic packaging;
- road builders;
- mechanics;
- car cleaners;
- graffiti removers;

[548] Health Council of the Netherlands. Occupational exposure to organic solvents: effects on human reproduction. The Hague: Health Council of the Netherlands, 2008; publication no. 2008/11OSH, available at https://www.gezondheidsraad.nl/sites/default/files/200811osh.pdf

- photographers.

However, the report goes on to state that *"Since the 1970s the use of ethylene glycol ethers EGME and EGEE has decreased dramatically and nowadays contributes less than 5% to the European usage of glycol ethers"*.

A report issued by the WHO[549] in 2009 identified that "A voluntary programme to control the application and use of 2-ethoxyethanol and 2-ethoxy-ethyl acetate within the EU has restricted their sale for use in consumer goods and household products, cosmetics, pesticide formulations, pharmaceutical preparations and medicines, photo-resist mixtures for semiconductor fabrication and other applications where exposure is poorly controlled (BfR, 2003[550])."

Consultation with companies has identified the following uses:

- Laboratory activities (e.g. quality control and/or research and innovation)

It is noted that 2-ethoxyethanol, when used in laboratory tests and R&D, like many other substances is only used for specific functions and research when relevant to the objective of the research. As such, it is not in constant use and may be used for some period, but then not for some time until a particular piece of research or development requires it.

A report from ECETOC appears to suggest that the use of EGEE and EGEEA may have been restricted to jet fuel de-icing and pharmaceutical production in the EU[551] by 2005.

Table X15-8: 2-Ethoxyethanol – summary of sectors and uses		
Sector	**Uses and/or activities**	**Notes (NACE codes, etc.)**
R&D	Used in scientific research and development; used in laboratory chemicals;	M72: Scientific research and development
Chemicals manufacture	used in laboratory chemicals used in varnish removers, lacquers,	C20: Manufacture of chemicals and chemical products C20.4: Manufacture of soaps and detergents, cleaning and polishing preparations, perfumes and toilet preparations
Printing	used as a solvent (used to dissolve printing inks)	C18.1: Printing and service activities related to printing
Semiconductor industry		C26.11: Manufacture of electronic components and boards
Jet fuel de-icing		
Pharmaceutical production		

[549] Concise International Chemical Assessment Document 67, SELECTED ALKOXYETHANOLS: 2-ETHOXYETHANOL AND 2-PROPOXYETHANOL, WHO 2009 accessed 22/08/2018 at: http://www.who.int/ipcs/publications/cicad/ethoxy_propoxyethanol.pdf

[550] BfR (2003) *2-Ethoxyethanol*. Berlin, Bundesinstitut für Risikobe-wertung (Federal Institute for Risk Assessment).

[551] European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC). 2005. *The Toxicology of Glycol Ethers and Its Relevance to Man (fourth edition) Volume I. Technical Report No. 95*, 16:16. Brussels:ECETOC.

Nature of exposure

Consultation with companies has indicated certain processes where potential exposure can occur:

- Filling of boilers/tanks
- Collection of substance and bottling

The 2008 risk assessment report identified a limited number of activities where potential exposure could occur in production and processing as a chemical intermediate as follows:

- Drumming
- Loading
- Cleaning
- Maintenance

Under REACH registration, The substance is used in the following PROC codes, with exposure potential for PROCs 3-15, so protective measures may be needed to reduce exposure:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 5: Mixing or blending in batch processes;
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities;
- PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing); and
- PROC 15: Use as a laboratory reagent.

X15.4 Exposed workforce

X15.4.1 Total number of exposed workers

Based on the information provided above, it appears that there are very limited uses of 2-ethoxyethanol, with the substance used primarily in the de-icing of airplanes and as an intermediate in chemical production.

EU labour statistics[552] estimate approximately 139,000 airport employees might be engaged in aircraft maintenance (79,000) and aircraft services (60,000). A best guess estimate is that there are approximately 1390 employees (rounded to 1,400) engaged in de-icing (1% of aircraft maintenance/aircraft services) in EU.

[552] Study on employment and working conditions in air transport and airports Final Report, October 2015 DG MOVE, European Commission https://ec.europa.eu/transport/sites/transport/files/modes/air/studies/doc/2015-10-employment-and-working-conditions-in-air-transport-and-airports.pdf

Due to the absence of any information identified through literature review and consultation regarding the number of workers potentially exposed to 2-ethoxyethanol in other sectors, a number of assumptions have been made in order to calculate the number of cases of different health effects arising from exposure from other uses of 2-ethoxyethanol.

Based on the number of companies in other sectors assumed to be using the substance (lower bound is 300, upper bound is 600), it is assumed that:

- The proportion of female employees of child bearing age in companies using 2-ethoxyethanol is the same as for the C:20 Manufacture of chemicals and chemical products sector as a whole;
- Female employees of child bearing age are spread equally across all companies using 2-ethoxyethanol in the C:20 Manufacture of chemicals and chemical products sector;
- Female employees potentially exposed are 1% of those employed.

Employment data from Eurostat for the C:20 Manufacture of chemicals and chemical products sector for 2016 has been used to generate the following estimates in sectors other than the airplane de-icing sector.

Table X15-9: Female employees potentially exposed to 2-ethoxyethanol in sectors other than de-icing	
Year	2016
No. of companies in C:20 Manufacture of chemicals and chemical products sector	29,590
Female workers	296,900
Male workers	934,500
Female Employees per company	10
No. female employees in co.s using 2EE [LOW Estimate, 300 companies]	3,010
No. female employees in co.s using 2EE [HIGH Estimate, 600 companies]	6,020
No. male employees in co.s using 2EE [LOW Estimate, 300 companies]	9,474
No. male employees in co.s using 2EE [HIGH Estimate, 600 companies]	18,949
No. female employees potentially exposed [LOW Estimate, 300 companies]	30
No. female employees potentially exposed [HIGH Estimate, 600 companies]	60
No. male employees potentially exposed [LOW Estimate, 300 companies]	95
No. male employees potentially exposed [HIGH Estimate, 600 companies]	189

X15.5 Exposure levels

X15.5.1 Current exposure levels

The literature review has not identified any recent data on measurement of exposure levels in recent years, and this is assumed to be due, at least in part, to the significant decline in the use of the substance in the EU. Much of the data comes from studies carried out in the 1990s and 2000s, with a Draft EU Risk Assessment Report[553] published in 2008 pulling together many of the results.

The assessment identified production and further processing as an intermediate as being relevant scenarios for occupational exposure and provided information from the only producer (since 1998) on inhalation exposure measurements from 1998 to 2006 as follows:

- < 0.01 mg/m³ to 5.3 mg/m³ (TWA, 96 samples), with 95th percentile of 3.0 mg/m³.

[553] European Union Risk Assessment Report - 2-Ethoxyethanol, Human Health only. Draft of October 2008, accessed at: https://echa.europa.eu/documents/10162/8df7f6fd-9268-4d0a-a881-f4cad9bb6df0

The report's conclusion was that based on the measurement results, an 8h TWA of 3.0mg/m3 was considered a reasonable worst case scenario. It noted that there were high levels of protection of workers in the large-scale chemical industry, further justifying this exposure level as a worst case scenario. It further noted, based on information from the manufacturer, that production was limited to a single period of only 10-15 days per year.

Regarding dermal exposure, production was observed as taking place primarily within closed systems and that use of PPE was highly accepted in the large-scale chemical industry. Safety data sheets indicated that appropriate gloves were worn and that low levels of dermal exposure were to be expected. The assessment went on to use a dermal exposure (based on the EASE model) of: 21 mg/person/day.

Additional exposure information has been identified from a number of other sources, including a report on workplace exposure published by the Hauptverband der gewerblichen Berufsgenossenschaften in August 2000[554].

Table X15-10: 2-Ethoxyethanol – average exposure levels per shift[555]					
Company type/Work area	Measurements	Companies	50% value	90% value	95% value
	Number	Number	mg/m³	mg/m³	mg/m³
Paint manufacture	34	18	3	17	25
- Without local exhaust ventilation	15	10	3	18	25
- With local exhaust ventilation	18	9	3	14	22
Manual coating (excluding spraying)					
- All measurements without local exhaust ventilation	35	15	*	11	44
Manual coating (spraying)	123	67	*	9	21
- Without local exhaust ventilation	25	11	*	8	17
- With local exhaust ventilation	91	54	*	11	22
Mechanical coating, printing	193	75	*	15	35
- Without local exhaust ventilation	95	38	*	14	28
- With local exhaust ventilation	94	44	*	14	29
Cleaning processes	43	25	*	5	10
- Without local exhaust ventilation	19	12	*	6	28
- With local exhaust ventilation	23	14	*	5	6
*Value < analytically detectable concentration of 0.5mg/m³ for a two-hour sampling period.					

[554] BGAA-Report 1/99e Existing commercial chemicals – Exposure at the workplace: Contributions to the assessment of the risk of chemical substances at the workplace under the EU programme on existing chemicals. Hauptverband der gewerblichen Berufsgenossenschaften (HVBG August 2000)

[555] 548 measurements analysed from around 210 companies in the print manufacturing, plastics, rubber, ceramics, glass, metalworking/mechanical engineering, electronic or/precision mechanics, printing/paper processing and construction industries and other areas.

Table X15-10: 2-Ethoxyethanol – average exposure levels per shift[555]					
Company type/Work area	Measurements	Companies	50% value	90% value	95% value
	Number	Number	mg/m³	mg/m³	mg/m³
% values: These figures mean that 50%, 90% or 95% of all available exposure measurements are below the prescribed limit, while the remaining 50%, 10% or 5% are above this limit. The German limit value for 2-Ethoxyethanol is 75 mg/m³, 20ml/m³ (MAK)					

For many of the company type/work areas, measurements below the analytically detectable concentration were as follows:

- Manual coating (excluding spraying): 88%
- Manual coating (spraying): 86%
- Mechanical coating, printing: 80%
- Cleaning processes: 81%

Further exposure measurement results were identified in a publication by ECETOC in 2005 and are set out in Table X15-11.

Time-weighted average (TWA) 2-ethoxyethyl acetate (EGEE-Ac) exposures of 12 ppm (range, 2.9–34 ppm) were found for press operators during production runs in a large format silk-screening operation. In 30 employees, biological monitoring yielded adjusted urinary 2-ethoxyacetic acid (EAA) concentrations of 1.1–27 mg/g creatinine. Assuming an average creatinine excretion rate of 800 mg/day, then the equivalent urinary EAA quantity would be in the range of 0.88 to 21.6 mg/day[556]. The total amount inhaled assuming 10 m³/workday is in the range of 0.09 to 2.16 mg/m3 (Table X15-11) or at the most < 1 ppm. Please note that these numbers do not correspond with the maximum exposure as measured, 34 ppm, dose as measured via urinary EEA is 40 fold less, contrary to results below.

Table X15-11: Occupational exposure to 2-ethoxyethyl acetate (EGEE-Ac)[556]							
	Adjusted urinary 2-ethoxyacetic acid (EAA) concentrations mg/g creatinine	Average creatinine excretion rate (mg/day)[557]	Equivalent urinary EAA quantity mg/day	Total amount inhaled (mg/m3)	Geomean (mg/m3)	Reference	Remarks
Min	1.1	800	0.88	0.09	0.44	Lowry LK et al 1993	TWA 2-ethoxyethyl acetate exposures of 12 ppm (range, 2.9–34 ppm)
Max	27	800	21.6	2.16			

[556] Lowry LK, Stumpp DA, Orbaugh C, Rieders F. 1993. Applications of biological monitoring in occupational health practice: practical application of urinary 2-ethoxyacetic acid to assess exposure to 2-ethoxyethyl acetate in large format silk-screening operations. Int Arch Occup Environ Health 65(1 Suppl):S47–S51. https://link.springer.com/article/10.1007/BF00381307

[557] https://en.wikipedia.org/wiki/Creatinine accessed on 07/10/2018

Table X15-12: Exposure measurement results in a publication by ECETOC in 2005				
Sector/substance	**Low (mg/m3)**	**High (mg/m3)**	**Other (mg/m3)**	**Reference**
Manufacture of glycol ethers in European plants (EGEE)	0.04	24.3		ECETOC, 1985
Printing, plants in Belgium (EGEE)	0.7	182.0	9.8 (geometric mean)	Veulemans et al 1987
Printing, plants in Belgium (EGEEA)	0.3	186.8	16.4 (geometric mean)	Veulemans et al 1987
Painting, plants in Belgium (EGEE)	1.4	210.3	9.5 (geometric mean)	Veulemans et al 1987
Painting, plants in Belgium (EGEEA)	1.2	78.6	9.7 (geometric mean)	Veulemans et al 1987
Car repair, plants in Belgium (EGEEA)	1.5	42.1	8.9 (geometric mean)	Veulemans et al 1987
Various, plants in Belgium (EGEE)	3.1	1,224 [a]	17.1 (geometric mean)	Veulemans et al 1987
Various, plants in Belgium (EGEEA)	0.6	819.5 [a]	9.9 (geometric mean)	Veulemans et al 1987
Semi-conductors (EGEE)			2.06 (ave. concentration)	Paustenbach, 1988
Semi-conductors (EGEE)			0.27 (ave. concentration)	Paustenbach, 1988
Varnish production (EGEE)	0.4	29.2	10.5 (mean)	Angerer et al, 1990
Varnish production (EGEEA)	<0.5	61	14.8 (mean)	Angerer et al, 1990
Airline maintenance, USA (EGEEA)			65.4 (15 mins)[b]	Piacitelli et al, 1990
Aerospace, USA (EGEE)			≤0.82	Piacitelli et al, 1990
Aerospace, USA (EGEEA)			≤1.26	Piacitelli et al, 1990
Electronics, USA (EGEEA)			≤0.11	Piacitelli et al, 1990
Airline maintenance, USA (EGEEA)	1.59	14.8		Piacitelli et al, 1990
Coating manufacture, USA (EGEEA)	0.38	1.92		Piacitelli et al, 1990
Automotive manufacture, USA (EGEEA)	≤0.11	0.27		Piacitelli et al, 1990
Glycol ether manufacturing, USA (EGEEA)	≤0.11	2.4		Piacitelli et al, 1990
Microelectronics manufacture (EGEEA)	0.005	3.5		Hallock et al, 1993
Silk-screen painting (EGEEA)	16	187		Lowry et al, 1993
Varnish production (EGEE)	<2.2	57	<0.4 – 23 (different day)	Söhnlein et al, 1993
Paint strippers, painters (EGEEA)	81	150	110 ± 29 (mean ± sd[c])	Vincent et al, 1994
Microelectronics manufacture (EGEEA)			0.35 ± 0.81 (mean ± sd[c]) 0.12 ± 0.02 (geometric mean ± sd[c])	Hammond et al, 1996
Aerospace (EGEEA)	29.7	151.7	81.3 (mean)	Vincent et al, 1996
Silk screen printing (EGEEA)	0.5	113	14.3 (mean)	Vincent et al, 1996
Paint and lacquer manufacture (EGEE)			0.1 (mean)	Wesolowski and Gromiec, 1997[d]
Paint and lacquer manufacture (EGEEA)			0.1 (mean)	Wesolowski and Gromiec, 1997[d]

Table X15-12: Exposure measurement results in a publication by ECETOC in 2005				
Sector/substance	**Low (mg/m3)**	**High (mg/m3)**	**Other (mg/m3)**	**Reference**
Shipyard painters (EGEEA)	Not detected Not detected	44.5 100.6	9.9 (mean, low exposure[e]) 16.5 (mean, high exposure[e])	Kim et al, 1999

[a] The study indicated that no information to explain these high results was noted. It went on to say that most personal exposure levels were far below occupational exposure limits in place at the time. The threshold limit value for EGEE was 19mg/m^3 and for EGEEA it was 27mg/m^3 (1984)
[b] This was noted for spray painting in airline maintenance, but in this case, respiratory protection was observed
[c] standard deviation
[d] Results for a range of types of plant were almost all the same, with only the result for airtight mill for EGEEA (0.3mg/m3) differing. The types of mill were: airtight mill, old mill (limited space), non-airtight mill (primitive solvent handling), small plant (ball mill, old resin plant), modern plant (high volume production
[e] Two groups of shipyard workers were tested, with one group experiencing low exposure and the other high exposure to EGEEA.
Note: The majority of results are indicated for long term exposure (up to 8-h TWA concentration, with some shorter exposures indicated
Source: The above data and references are cited in "The Toxicology of Glycol Ethers and its Relevance to Man, Vol I, ECETOC 2005", available at: http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-095-Vol-I.pdf

In an exposure survey of 17 workers conducted in a varnish plant in Germany, the investigators found that 12 varnish production workers were exposed to an average 2-ethoxyethanol concentration of 2.8 ppm (or 11.08 mg/m3) (Angerer et al 1990[558]). Urine samples taken pre-shift and post-shift were analysed for EAA and other metabolites of glycol ethers. The average post-shift concentration of EAA was 168 mg/L[558]. This translates into total inhaled amount (Table X15-13) of 20.14 mg/m3 (approx. 5 ppm) in contrast to 0.44 mg/m3 in the study by Lowry K et al 1993[556] (i.e. 46 fold higher exposure). Please also note that the calculated concentration (pre-shift concentration not available and hence not deducted from the post-shift concentration) is approximately 2 times higher than the actual exposed concentration. These data and the data above appear to indicate that urinary EAA might not be the most appropriate BLV for ethoxyethanol.

Table X15-13: Occupational chronic exposure to Ethoxyethanol[558]

Urinary EAA quantity mg/l (post-shift)	Urinary EAA quantity mg/day	Total amount inhaled (mg/m3)	Reference	Remarks
167.8	201.36	20.14	Angerer J et al 1990	Average 2-ethoxyethanol exposure 2.8 ppm

The potential for testicular [toxicity] in a group of workers exposed to 2-ethoxyethanol vapours was assessed by Clapp et al. (1987) and Ratcliffe et al. (1989)[559]**Error! Bookmark not defined.**. Exposure levels ranged from not detectable to 24 ppm (88 mg/m3, assuming 25°C and 760 mm Hg), with average levels less than 6 ppm (22 mg/m3) in one building and 11 ppm (41 mg/ m3) in a second building**Error! Bookmark not defined.**. Exposure occurred by inadvertent skin contact, inhalation or by airborne vapour condensing on the skin. Ratcliffe et al. (1989) obtained semen samples from 37 exposed and 39 [control] workers.

It is presumed (ECHA SVHC record)[560] that the only presently approved use of 2-ethoxyethanol is as an airplane de-icer. In aircraft de-icing, two distinct procedures, the One-Step and the Two-Step procedure are followed[561]. One of these two procedures is chosen depending on the current overall situation.

In One-Step Operation, de-icing and anti-icing are carried out in one operation and is recommended when there is only low contamination, no precipitation and if the time interval between the beginning of the de-icing/anti-icing and take-off is 35 minutes at the most. During the one-step operation a water/Type I mixture, heated to 60 °C at least (temperature at the nozzle), is usually used. The aircraft is only considered to be sufficiently protected when at least 1 l/m² of Type I[562] is applied on the aerodynamically critical surfaces.

In 2 Two-Step Operation, anti-icing takes place in two steps if the aircraft is severely contaminated and there is precipitation and/or take-off is not possible within a short period of time due to slot,

[558] Angerer J, Lichterbeck E, Begerow J, Jekel S, Lehnert G. Occupational chronic exposure to organic solvents. XIII. Glycolether exposure during the production of varnishes. 1990. Int Arch Occup Environ Health 62(2):123–126 https://link.springer.com/article/10.1007/BF00383588

[559] Ratcliffe JM, Schrader SM, Clapp DE, Halperin WE, Turner TW, Hornung RW. 1989. Semen quality in workers exposed to 2-ethoxyethanol. Br J Ind Med 46(6):399–406.

[560] https://echa.europa.eu/documents/10162/f25b7ab7-c339-4b4a-900b-7a2d38c32c1f

[561] Aircraft De-Icing Manual 2017/2018 Flughafen Köln/Bonn GmbH; https://www.cologne-bonn-airport.com/uploads/tx_download/De-Icing_Manual_Cologne_Bonn_Airport_2017_-_2018_-_Edition_2.2.pdf

[562] The calculation formula for the Lowest Operational Use Temperature (LOUT) is as follows: Type I – unthickened fluid = freezing point of the fluid minus 10° C and Type II/III/IV – thickened fluid = freezing point of the fluid minus 7° C. A binding principle and rule is: If the LOUT is exceeded, there are no holdover times (protection time against re-icing), meaning that the protective effect of the fluid is NOT ensured.

traffic, etc., and/or precipitation until take-off is expected so that a thorough cleaning and longer protection until take-off is necessary. In order to remove contamination, heat and pressure are always necessary. This takes places in the first step with only heated water and Type I. As the mixing ratio depends on the temperature, the amount of Type I can be kept as low as possible by thinning the ratio, thus saving costs for the airline. The actual protection against re-icing takes place in the second step when Type II is applied.

In one study[563] de-icing operators were exposed to ethylene glycol. Ethylene glycol vapour concentrations did not exceed 22 mg/m^3 whereas mist samples ranged from 76 to 190 mg/m^3. Sampling periods were not more than 2 hours and averaged less than 1 hour. Concentrations ranged from 22 to 190 mg/ m^3 or 8 to 70 ppm. One can roughly postulate that equivalent exposure to 2-ethoxyethanol would results in similar concentrations of 8 to 70 ppm ignoring physicochemical considerations. These data exceed several of the occupational exposure standards, at a minimum on an excursion basis. On a TWA-8 hour (assuming a 4 hr workday) exposure would be rated at 4 ppm with excursions to 70 ppm. Equivalent exposures would be 16 mg/m^3 to 280 mg/m^3. These data are considered very conservative; the actual TWA8 on an annual basis could be much smaller.

It is noted however that this study was carried out in 1997, significantly prior to the adding of 2-ethoxyethanol to the Candidate list in 2010 and over 20 years ago. The regulatory scrutiny that has occurred leading up to the inclusion in the list and subsequently will most likely have led to increased safety measures being adopted.

Conclusion on exposure levels

Given the measured exposure examples detailed above, whilst some exposure has been measured at higher levels in some of the studies, the vast majority of measurements (particularly when considering mean values from a range of studies across sectors) are below many of the OEL levels in Member States, and are below the threshold levels for almost all of the health effects identified in Table X15-5. This would imply that a figure of 19mg/m^3 (the highest OEL in Member States identified could be considered the worst-case scenario for most situations.

Regarding manufacture of 2-ethoxyethanol, the Brief Profile generated by ECHA[564] indicates that 2-ethoxyethanol is used in “closed processes with no likelihood of exposure”.

Consultation has identified that there is potentially some exposure to 2-ethoxyethanol in the waste treatment sector (Treatment and Elimination of Non-Hazardous Waste in 2015), but measured data suggest that exposures are very low (less than a maximum of 0.71 mg/m^3, with an arithmetic mean of 61 measurements of 0.07mg/m^3, which is well below even the lowest threshold of 3mg/m^3 identified in Table X15-11 above and even more significantly lower than the EU indicative OEL of 8mg/m^3.

It is noted that in 2003, OSHA[565] in the United States withdrew its proposed standard on Occupational Exposure to 2-Ethoxyethanol and its acetates since production and use had either ceased or was virtually limited to "closed systems" where exposure levels more than 10 years ago already were at or below the proposed permissible exposure limits (PELs). It stated that there are few, if any, remaining opportunities for workplace exposure to these glycol ethers and little or no potential for exposure in the future because of the availability of less-toxic substitutes.

[563] Gerin et al, Int. Arch. Occup. Environ. Health 1997; 69(4):255-265. A study of ethylene glycol exposure and kidney function of aircraft de-icing workers. https://www.ncbi.nlm.nih.gov/pubmed/9138000

[564] https://echa.europa.eu/brief-profile/-/briefprofile/100.003.459

[565] https://www.osha.gov/laws-regs/federalregister/2003-12-31

X15.6 Current Risk Management Measures (RMMs)

X15.6.1 Overview of RMMs

Risk management measures are recommended in REACH registration information for 2-ethoxyethanol and include measures set out in Table X15-14 below.

Table X15-14: RMMs recommended for 2-ethoxyethanol	
Area	**Measure**
Closed systems/engineering controls	Use in a closed-system
	Sufficient ventilation to remove and prevent build-up of vapours, dusts or fumes that could be generated during handling or thermal processing
Organisational measures	Only use under strictly controlled conditions
	Do not eat or drink; do not smoke when using the substance
	Wash hands before breaks and at the end of the work day
	Keep working clothes separate; vacuum clean contaminated clothing; take off contaminated clothing immediately and use again only after washing
	Store protective clothing separately;
	Avoid contact with eyes and skin
	Keep away from foodstuffs, beverages, and feed
Respiratory protection	Respirators should be used (CEN 143 or 149) where the airborne concentrations are expected to exceed the exposure limit Use a respiratory filter device for brief exposure or low pollution; Use a respiratory protective device which is independent of circulating air for longer or intensive exposure; Short term filter device: Filter A; Only use breathing equipment for handling the residual risk where all other risk minimising measures have been carried out, such as local exhaust and/or retention
Eye protection	Eye protection/ Chemical googles as per a health and safety professional (OSHA (29 CFR 1910.133) or EN166 (Europe)). Tightly sealed goggles.
Hand, Skin and body protection	Impervious / protective gloves for prolonged contact (including instructions to wear other types than rubber gloves) Solvent resistant gloves; apply skin-cleaning agents and skin cosmetics after use of gloves The following materials are not suitable: Polychlorprene rubber (CR), nitrile rubber (NBR), Natural rubber (NR) and fluorocarbon rubber (FKM)
Source: ECHA (2018): 2-ethoxyethanol REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14915/9	

X15.6.2 Voluntary industry initiatives

2-ethoxyethanol is a glycol ether and Glycol Ethers[566] are a product working group of the Oxygenated Solvent Producers Association (OSPA) which brings together producers of oxygenated solvents in Western Europe. OSPA is a sector group of CEFIC (the European Council of the Chemical Industry). They highlight that for a range of substances that are produced commercially, including EGEE, industry

[566] http://www.glycol-ethers.eu/index.php/about-us/aboutus

has in place a charter to make sure that the substances are only sold into compliant applications and uses where strict exposure control measures are in place. The Charter is set out in the Box below.

Box X15-1 Glycol Ethers Charter

Oxygenated Solvents Producers Association (OSPA)

The European producers of Glycol Ethers, members of OSPA, wish to recall by this charter the commitments and actions that are being undertaken to avoid the risks linked to glycol ethers classified toxic for reproduction.

GLYCOL ETHERS

Glycol Ethers are solvents which constitute a varied family of more than 30 different substances. They have similar physical properties but do not demonstrate all the same technical characteristics nor the same toxicity profiles. This is why they are not interchangeable and this is why a large number of Glycol Ethers are put on the market for sale. Some Glycol Ethers are sold in large; others only in low quantities and several are even not produced at all.

THE GLYCOL ETHERS CLASSIFIED TOXIC FOR REPRODUCTION

Eight glycol ethers have been classified for reproductive toxicity; seven (EGME, EGEE, EGDME, DEGDME, TEGDME, 1PG2ME, 1PG2MEA) are classified as Category 1B and one (DEGME) as category under the CLP Regulation. Of the seven glycol ethers classified for reproductive toxicity as category 1B under CLP and carrying the Hazard Phrase H360 -may damage fertility or the unborn child- only three of them are produced commercially in the EU: ethylene glycol methyl ether (EGME), ethylene glycol dimethyl ether (EGDME) and diethylene glycol dimethyl ether (DEGDME). Methoxy-2-propanol-1 (1PG2ME) is never produced as such, yet occurs as an impurity at the production of methoxy-1-propanol-2 (PGME).

The OSPA Charter for the consumers / workers protection

Since 1996, the producers have signed a voluntary agreement on the commercialisation of these substances that was formalised and applied progressively via a charter. This agreement preceded the legislation that banned the sale of products classified toxic for reproduction, category 1 and 2 (amended law of 7 August 1997 concerning the limitations on the marketing and use of products containing certain dangerous substances).

The Charter forbids, under penalty of non-delivery, all uses of glycol ethers classified as reprotoxic in any product sold to the public and strictly limits the use of glycol ethers classified toxic for reproduction category 2 to industrial applications, for which no substitute has been found so far. ALL customers must ensure that Occupational Exposures/Emissions are within the legal constraints. The charter must be signed by buyers (from direct customers) as well as by any distributor involved. The producers oblige all buyers to annually reconfirm the application of the charter.

With the present document, the producers, members of OSPA, reconfirm their ongoing commitment to strictly apply all provisions of the 1996 charter.

THE GLYCOL ETHERS NOT CLASSIFIED TOXIC FOR REPRODUCTION

The producers are continuing their activities to improve the knowledge about the properties of these substances.

All producers confirm that the glycol ethers of the E series (derivates of ethylene glycol that are not mentioned above and which are commercialised for various applications) do not contain as an impurity any of the glycol ethers classified toxic for reproduction, category 2: EGEE, EGEEA, EGME, EGMEA, EGDME, DEGDME, TEGDME. Commercial preparations of methoxy-1-propanol-2 contain, as an impurity, the isomer méthoxy-2-propanol-1 called ß isomer. In pure form, this ß isomer is classified toxic for reproduction category 2. All producers from glycol ethers of the P series (derivates of propylene glycol) confirm that for all commercial products the ß

isomer concentration is clearly below the level of 0.3%, the classification limit set by the legislation. The same reasoning applies for the acetate of methoxy-1-propanol-2 and its ß isomer. Furthermore, toxicity tests completed on different glycol ethers of the P-series have not led to any classification for reprotoxicity.

The charter indicates that EGEE is no longer commercially produced in the EU and that all customers must ensure that occupational exposures/emissions are within legal constraints. Of particular note is the charter's inclusion:

The Charter forbids, under penalty of non-delivery, all uses of glycol ethers classified as reprotoxic in any product sold to the public and strictly limits the use of glycol ethers classified toxic for reproduction category 2 to industrial applications, for which no substitute has been found so far.

X15.7 Market analysis

Concentrating on the chemicals sector, since the use of 2-ethoxyethanol is primarily as a chemical intermediate, Eurostat data indicates that there were the following numbers of companies operating in the EU under NACE Code C20: Manufacture of chemicals and chemical products in 2016.

Table X15-15: Manufacture of chemicals and chemical products				
TOTAL	Micro	Small	Medium	Large
29,590	19,580	6,240	2,950	830

2-ethoxyethanol is a glycol ether within the solvents family of chemicals, but Eurostat data does not provide sufficient granularity to estimate the number of companies involved in the manufacture of solvents, let alone glycol ethers.

It has not been possible to identify the number of companies using either solvents more generally or glycol ethers from literature review and internet searches. Consultation with industry associations and companies did not indicate widespread use of the substance. It is noted that solvents are only a proportion of the overall chemicals market, and glycol ethers are a proportion of the solvents market. Section X15.3.1 indicates that EGME and EGEE use has decreased dramatically and nowadays represented less than 5% of the European usage of glycol ethers in 2008. This number is likely to have declined again since then and only a handful of companies are likely to remain which use 2-ethoxyethanol.

As indicated, previously, the number of uses of 2-ethoxethanol has decreased substantially since the 1990s and there are apparently very few, if any, outside its current use in products used for de-icing airplanes and as a chemical intermediate. Only the larger airports are likely to operate de-icing of airplanes (smaller airports usually close during severely inclement weather) and warmer weather in southern EU Member states would also mean that it is not required.

It is therefore assumed for the purposes of this study:

- de-icing is carried out by airports and not individual airlines
- approximately 100 airports operate de-icing facilities

In terms of other companies using 2-ethoxyethanol, the following assumptions are made

- A lower bound estimate of 300 companies
- An upper bound estimate of 600 companies

In total, the study assumptions for the number of companies suing 2-ethoxyehanol in the EU are as follows:

- Lower bound: 400
- Upper bound: 700

It is recognised that there is significant uncertainty in these assumptions and the number could be both higher and lower.

Some general characteristics of the relevant sectors are given below. These sectors are:

- C18.1: Printing and service activities related to printing
- C20.1 Manufacture of basic chemicals, fertilisers and nitrogen compounds, plastics and synthetic rubber in primary forms
- C20.4: Manufacture of soaps and detergents, cleaning and polishing preparations, perfumes and toilet preparations
- C26.11: Manufacture of electronic components and boards
- M72: Scientific research and development
- Jet fuel de-icing: n/a on Eurostat
- Pharmaceutical production: n/a on Eurostat

X15.7.1 Number of SMEs in each sector

Table X15-16: Number and proportion of SMEs by size of enterprise and sector									
Sector	TOTAL	Micro		Small		Medium		Large	
	No. firms	No. firms	% of total	No. firms	% of total	No. firms	% of total	No. firms	% of total
C18.1	**112,440**	100,320	89%	10,960	10%	1,690	2%	110	0%
C20.1	**8,980**	5,190	58%	2,010	22%	980	11%	360	4%
C20.4	**9,560**	7,090	74%	1,600	17%	680	7%	170	2%
C26.1	**10,170**	7,230	71%	2,040	20%	700	7%	190	2%
M72	**65,750**	59,950	91%	4,140	6%	1,330	2%	330	1%
Source: Eurostat's Structural Business Statistics database									

X15.7.2 Average turnover by size of enterprise

Table X15-17: Average turnover by sector and size of enterprise, 2016												
Sector	Micro			Small			Medium			Large		
	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m
C18.1	15,478	100,320	0.15	23,119	10,960	2.11	26,407	1,690	15.63	15,388	110	139.89
C20.1	6,854	5,190	1.32	19,422	2,010	9.66	68,909	980	70.32	234,358	360	650.99
C20.4	2,315	7,090	0.33	5,848	1,600	3.66	17,418	680	25.61	47,164	170	277.44
C26.1	2,174	7,230	0.30	5,765	2,040	2.83	10,697	700	15.28	39,733	190	209.12
M72	-	59,950	-	-	4,140	-	-	1,330	-	-	330	-
Source: Eurostat's Structural Business Statistics database												

X15.7.3 R&D expenditure

Table X15-18: Business expenditure on R&D per sector (in € million), EU28		
Sector	**Data availability**	**R&D expenditure (in €m)**
C18.1	C18	214.8
C20.1	C20	6,659.7
C20.4	C20	6,659.7
C26.1	C26.1	2,771.2
M72	M72	17,981.8
Source: Eurostat Notes: EU28 totals do not include data for some member states, due to confidentiality.		

X15.8 Burden of ill health

X15.8.1 Cases of ill health

Airplane de-icing

Using the estimate above of approximately 1,400 workers being involved in the de-icing of planes in the EU, based on Eurostat estimates, 23% of workers in the chemicals sector are women of childbearing age. However, this figure includes all workers in the sector, including administrative workers, management etc. and not just those that are likely to have some exposure. It is also noted work involving de-icing of planes takes place in potentially hardship conditions (due to extreme weather conditions) and whilst no estimates of women workers specifically involved in de-icing planes have been identified, industry estimates do vary, with an association representing cable manufacturers suggesting during consultation for this study (albeit involving the use of a different reprotoxic substance), that women represent only 10% of the production workforce.

It is also noted that work involving de-icing of planes is very seasonal and workers would only be involved in this for a limited window each year in most of the EU. Any developmental effects are likely to be dependent on when the mother is pregnant and if this coincides with the coldest months of the year.

Consequently, this study has adopted a figure of 10% of the workforce as being women of child bearing age (15-49).

Based on a report, Macklon et al[567] in the Netherlands, it is estimated that of all conceptions, 30% of conceptions result in implantation failure and another 30% result in early pregnancy loss and 30% result in a live birth (with the remaining 10% resulting in miscarriage). Interpreting a decrease in the number of live foetuses as an early pregnancy loss, these estimates have been used to calculate the number of cases of the different health effects arising from exposure to 2-ethoxyethanol as illustrated in A14-19 below. Two scenarios have been developed, with the first applying the EU indicative OEL of 8mg/m^3 for the level of exposure, and the second utilising the highest OEL identified in Member States of 19mg/m^3. Given the measured exposure examples detailed previously, whilst some exposure has been measured at higher levels in some of the studies, the vast majority of measurements (particularly

[567] Conception to ongoing pregnancy: the 'black box' of early pregnancy loss, N.S. Macklon, J.P.M. Geraedts and B.C.J.M Fauser, Human Reproduction Update, Vol 8, No.4, 2002

when considering mean values from a range of studies across sectors) are below this level, and would imply that a figure of 19mg/m^3 could be considered the worst-case scenario for most situations.

Table X15-19: Cases suffering health effect arising from exposure per year (based on 10% of workforce being women aged 15-49)						
Health effect	**Detail**	**Threshold**	**DRR**	**Exposed workers**	**Concentration**	**Cases**
Spontaneous abortion (early pregnancy loss)	Decreased number of live foetuses	3mg/m^3	y=-0.49x+1.47	140 F	Low: 8mg/m^3	0.03
				140 F	High: 19mg/m^3	0.09
Development	Increased no. of foetuses with limb malrotation	3mg/m^3	y=0.13x-0.39	140 F	Low: 8mg/m^3	Club foot: 0.002
						Limb: 0.006
				140 F	High: 19mg/m^3	Club foot: 0.005
						Limb: 0.0204

In the event that a figure of 23% were to be adopted for the percentage of women workers of child bearing age, the number of cases would be slightly higher as illustrated in the table below.

Table X15-20: Cases suffering health effect arising from exposure per year (based on 23% of workforce being women aged 15-49)						
Health effect	**Detail**	**Threshold**	**DRR**	**Exposed workers**	**Concentration**	**Cases**
Spontaneous abortion (early pregnancy loss)	Decreased no. of live foetuses	3mg/m^3	y=-0.49x+1.47	322 F	Low: 8mg/m^3	0.07
				322 F	High: 19mg/m^3	0.21
Development	Increased no. of foetuses with limb malrotation	3mg/m^3	y=0.13x-0.39	322 F	Low: 8mg/m^3	Club foot: 0.004
						Limb: 0.015
				322 F	High: 19mg/m^3	Club foot: 0.011
						Limb: 0.047

Cases arising from the use of 2-Ethoxyethanol in other sectors

The following two tables present the number of cases for the different health effects likely to arise from exposure to 2-ethoxyethanol from its use in intermediates under the low and high scenarios.

Table X15-21: Cases suffering health effect arising from exposure per year in other sectors- LOW Scenario						
Health effect	**Detail**	**Threshold**	**DRR**	**Exposed workers**	**Concentration**	**Cases**
Spontaneous abortion (early pregnancy loss)	Decreased number of live foetuses	3mg/m^3	y=-0.49x+1.47	30 F	Low: 8mg/m^3	0.0062
				30 F	High: 19mg/m^3	0.02
Development	Increased no. of	3mg/m^3	y=0.13x-0.39	30 F	Low: 8mg/m^3	Club foot: 0.00033

Table X15-21: Cases suffering health effect arising from exposure per year in other sectors- LOW Scenario						
Health effect	**Detail**	**Threshold**	**DRR**	**Exposed workers**	**Concentration**	**Cases**
	foetuses with limb malrotation					Limb: 0.0014
				30 F	High: 19mg/m^3	Club foot: 0.001
						Limb: 0.0044

Table X15-22: Cases suffering health effect arising from exposure per year in other sectors- HIGH Scenario						
Health effect	**Detail**	**Threshold**	**DRR**	**Exposed workers**	**Concentration**	**Cases**
Spontaneous abortion (early pregnancy loss)	Decreased number of live foetuses	3mg/m^3	y=-0.49x+1.47	60 F	Low: 8mg/m^3	0.0125
				60 F	High: 19mg/m^3	0.04
Development	Increased no. of foetuses with limb malrotation	3mg/m^3	y=0.13x-0.39	60 F	Low: 8mg/m^3	Club foot: 0.00067
						Limb: 0.0027
				60 F	High: 19mg/m^3	Club foot: 0.002
						Limb: 0.009

EGEEA

As can be seen from Table X15-23 below, all of the thresholds for the different effects are above the highest OEL identified across the EU (19mg/m^3 in Hungary). Consequently, no cases of effects are expected as a result of exposure to EGEEA.

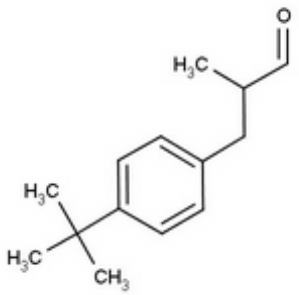
Table X15-23: Thresholds for different health effects identified from exposure to EGEEA		
Health effect	**Threshold (mg/m^3)**	**OELs (low – high)**
Increased post-implantation loss	436	8mg/m^3 – 19mg/m^3
Decreased mean no. of live foetuses	436	
Decreased mean total litter weight	436	
Increase in the rates of any skeletal defects	109	
Increase in the rates of external and visceral minor defects	436	
Decrease in foetal weight	109	
Cardiovascular malformation	41	

Annex 16 2-(4-tert-butylbenzyl)propinolaldehyde

X16.1 Introduction

X16.1.1 Relevant substance(s)

2-(4-tert-Butylbenzyl) propionaldehyde (TBP also known as Lilial or Lysmeral or Butylphenyl methylpropional, p-tert-Butyl-alpha-methylhydrocinnamaldehyde (BMHCA) or lily aldehyde) is a fragrance ingredient used in many cosmetics, fine fragrances, shampoos, toilet soaps and other toiletries.[568] Substance information is presented in the table below.

Table X16-1: Substance information	
Substance Name	2-(4-tert-butylbenzyl)propionaldehyde
Acronyms	4-*tert*-Butyl-α-methyl-benzenepropanal, 4-*tert*-Butyl-α-methyl-hydrocinnamaldehyde, Butylphenyl methylpropional, Lilial
EC Number	201-289-8
CAS number	80-54-6
Structure	
Source: ECHA (2018): 2-(4-tert-butylbenzyl)propionaldehyde Substance Information. Available at: https://echa.europa.eu/substance-information/-/substanceinfo/100.001.173	

X16.1.2 Hazard classification(s)

The substance is self-classified under the CLH. The notified reproductive classifications are:

- H360 (self): May damage fertility or the unborn child (Repr. 1B); and
- H361 (self): Suspected of damaging fertility or the unborn child (Repr. 2)

Other health classifications (self-classified) for the substance are:

- H302 (Acute Tox. 4): Harmful if swallowed;
- H315 (Skin Irrit. 2): Causes skin irritation; and
- H317 (Skin Sens. 1B): May cause and allergic skin reaction

X16.1.3 Existing OELs and BLVs

There are no OELs or BLVs in place for the substance.

[568] ECHA (2013): CLH Report 2-(4-tert-butylbenzyl)propinaldehyde. Available at: https://echa.europa.eu/documents/10162/2eff6c48-0950-4656-af10-342c574d5987

DNEL (Derived No Effect Level)

For workers, the DNELs are as follows: [569]

- Long-term systemic inhalation DNEL: 0.44 mg/m^3 (Overall assessment factor of 10, most sensitive endpoint: repeated dose toxicity); and
- Long-term systemic dermal DNEL: 1.79 mg/kg bw/day (Overall assessment factor of 40, most sensitive endpoint: repeated dose toxicity)

X16.1.4 Legislation other than CAD

REACH

The substance is not subject to restriction or authorisation under REACH.

Cosmetics Regulation

The substance, under Regulation (EC) No 1223/2009 on cosmetic products is regulated for labelling. When the substance is present in a concentration above 10 ppm for leave-on products and above 100 ppm for rinse-off products, the presence of the substance must be indicated in the list of ingredients.[570]

X16.2 Summary of health endpoints, thresholds and DRRs

X16.2.1 Relevant health endpoints

Relevant reproductive health endpoints

2-(4-tert-butylbenzyl) propionaldehyde, from its CLH reproductive classification may damage fertility or the unborn child. Relevant reproductive health effects, identified from literature review are presented in the following table along with the monetised health effect that may be used to value it.

[569] ECHA (2018): 2-(4-tert-butylbenzyl)propinaldehyde Registration Dossier- Toxicological Summary. Available at: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/13572/7/1

[570] Official Journal of the European Union (2009): Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R1223&from=EN

Table X16-2: Summary of reproductive health effects				
Health effect	Fertility/development		Male/ Female exposure	Monetisable effect correlate
	Fer	Dev		
Reduction in mean fraction of motile sperm in the cauda epididymis[571]	Fer		M	Impaired fertility - male
Increase in mean fraction of abnormal sperm[571]	Fer		M	Impaired fertility - male
Reduction in mean sperm head count in the cauda epididymis[571]	Fer		M	Impaired fertility - male
Testicular atrophy[572]	Fer		M	Impaired fertility - male
Reduction in mean implantation sites[571]	Fer		M/F	Impaired or reduced fertility male and female
Decreased litter size	Fer		M/F	Impaired fertility - male Impaired fertility - female
Increased number of stillborn pups[573]	Fer	Dev	M/F	Impaired fertility - male Impaired fertility - female
Decreased number of live born pups[573]	Fer		F	Spontaneous abortion or still birth
Decrease in viability index[573]		Dev	F	Spontaneous abortion or still birth
Decrease in mean number of implantation sites (P1)[574]	Fer		F	Impaired fertility offspring – female (but can only value males)

X16.2.2 Summary of thresholds and DRRs

The no effect thresholds (inhalation 8-hr TWA mg/m^3) and effect slopes, together with the maximum air exposure concentrations (8-hr TWA mg/m^3) for which the effect slopes are valid, are summarised below. For a more detailed overview of the approach to the derivation of these values, refer to Annex 1.

[571] ECHA (2018): REACH dossier for 2-(4-tert-butylbenzyl) propionaldehyde. Unnamed report, 2017a. Available at:https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/13572/7/9/2/?documentUUID=5e8708fc-7064-4a26-935d-76ae118c4448

[572] BASF SE (2006A): Summary of Results -Lysmeral and Lysmerylsaeure- Comparative Toxicity Study in Wistar rats- Administration by gavage over 2 weeks; 48S0369/01154 as cited in the CLH report for 2-(4-tert-butylbenzyl)propionaldehyde 2013. Available at: https://echa.europa.eu/documents/10162/2eff6c48-0950-4656-af10-342c574d5987

[573] ECHA (2018): REACH dossier for 2-(4-tert-butylbenzyl) propionaldehyde. Unnamed report 2011a. Available at: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/13572/7/9/2/?documentUUID=503dcb0f-eff2-43ae-be05-aca88ec7314a

[574] ECHA (2018): REACH dossier for 2-(4-tert-butylbenzyl) propionaldehyde. Unnamed report 2017b. Available at: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/13572/7/9/2/?documentUUID=30bcf702-e6a7-4770-ac61-304ca92b598c

Table X16-3: Effects, thresholds and DRRs				
Health effect	Threshold		Dose response curve	
	Converted (mg/m^3)	Upper range of applicability of slope	Converted (mg/m^3)	Slope ($\%/mg/m^3$)
Reduction in mean fraction of motile sperm in the cauda epididymis	17.5	52.5	35.0	1.71
Increase in mean fraction of abnormal sperm	17.5	52.5	35.0	1.9
Reduction in mean sperm head count in the cauda epididymis	17.5	52.5	35.0	-0.87
Testicular atrophy	43.8	87.6	43.8	0.75
Testicular atrophy	8.75	87.55	78.8	1
Reduction in mean implantation sites	17.5	52.5	35.0	-1.74
Decreased litter size	263	788	525	-0.01
Increased number of stillborn pups	263	788	525	4.00
Decreased number of live born pups	263	788	525	-0.08
Decrease in viability index	263	788	525	-0.09
Decrease in mean number of implantation sites (P1)	5.25	17.55	12.3	-1.13

X16.3 Relevant sectors, uses, and operations

The substance (which is also known as Lilial, Lysmeral, butylphenyl, methylpropional, p-tert-butyl-alpha-methylhydrocinnamaldehyde (BMHCA), and lily aldehyde) is used in fragrances. The substance is used in cosmetics (such as decorative cosmetics), personal care products (such as shampoos, toilet soups and other toiletries), and washing and cleaning products.

Other uses include in biocidal products, coatings and paints, fillers/plasters, ink/toners, polishes/wax blends and scented articles.[575] The substance is also listed as possibly being used in air care products and biocidal products.[576] In biocidal products, the substance is used as an active ingredient, for example in pest control products and disinfectants.[577]

The latest CLH report (2017) only lists uses of the substance in cosmetics, personal care products and washing/cleaning products with proposed concentration limits in the following products:

- Hydroalcoholic-based fragrances (such as aftershave, cologne, perfume, Eau de Toilette) with a concentration limit of 1.42%;
- Deodorants: concentration limit of 0.09%;
- Make up products (such as eye make-up, eyeliner, liquid foundation, mascara and make-up remover): concentration limit of 0.04%;
- Face cream: concentration limit of 0.05%;
- Hand cream: concentration limit of 0.05%;
- Body lotion: concentration limit of 0.06%;
- Hair styling: concentration limit of 0.04%; and

[575] ECHA (2013): CLH Report 2-(4-tert-butylbenzyl)propinaldehyde. Available at: https://echa.europa.eu/documents/10162/2eff6c48-0950-4656-af10-342c574d5987

[576] ECHA (2017): CLH report for 2-(4-tert-butylbenzyl)propionaldehyde. Dated December 13, 2017. Available at: https://echa.europa.eu/documents/10162/c4cf84f3-f8a1-33af-1a4c-fd278444547a

[577] Chemsafe (2018): Newsletter March 2018. Available at: https://www.chemsafe-consulting.com/wp-content/uploads/2018/03/03-2018-Newsletter_EN.pdf

- Bath products (such as shampoo, shower gels, shampoo and conditioner): concentration limit of 0.1%.

A summary of relevant sectors and use where occupational exposure to 2-(4-tert-butylbenzyl) propionaldehyde could occur are listed in the following table.

Table X16-4: 2-(4-tert-butylbenzyl)propionaldehyde – sectors and uses		
Sector	**Uses and/or activities**	**Notes (NACE codes, etc.)**
Personal care products	Used as a fragrance	C20.41 (manufacture of soaps and detergents, cleaning and polishing preparations, perfumes and toilet preparations)
Cosmetics	Used as a fragrance	C20.42 (manufacture of perfumes and toilet preparations)
Cleaning	Use as a cleaning agent	N81.2 (Cleaning activities)
Biocides	Used as an active ingredient	C20.2 (manufacture of pesticides and other agrochemical products)

X16.3.1 Operations for occupational exposure (PROC codes)

The uses by PROC codes of the substance in its REACH dossier are:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 4: Chemical production where opportunity for exposure arises;
- PROC 5: Mixing or blending in batch processes;
- PROC 7: Industrial spraying;
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities;
- PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing);
- PROC 10: Roller application or brushing;
- PROC 11: Non industrial spraying;
- PROC 13: Treatment of articles by dipping and pouring;
- PROC 14: Tabletting, compression, extrusion, pelletisation, granulation;
- PROC 15: Use as laboratory reagent; and
- PROC 19: Hand-mixing with intimate contact and only PPE available.

More specifically, PROC codes listed for uses by professional workers (use as cleaning agents) are:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions
- PROC 4: Chemical production where opportunity for exposure arises

- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities;
- PROC 10: Roller application or brushing;
- PROC 11: Non industrial spraying; and
- PROC 19: Hand-mixing with intimate contact and only PPE available.

From the PROC codes, there are a number of activities where exposure could occur; for example for PROC 7 (Industrial spraying); PROC 10 (Roller application or brushing); and PROC 11 (Non industrial spraying).

X16.4 Exposed workforce

X16.4.1 Total number of exposed workers

Through literature review, there is no publically available information on the number of exposed workers. The exposed workforce, can however, be estimated, for the purposes of this study, based on employment figures indirectly related to 2-(4-tert-butylbenzyl) propionaldehyde, and a number of assumptions based on available data. Male workers of reproductive age have been estimated for this substance as the modelled effect is male infertility. For each sector for calculating the number of exposed workers (Table X16-5), data from Eurostat has been used as the starting point and refined for each sector as discussed in the following sectors.

Manufacture of chemicals

For this sector for calculating the number of exposed workers, it has been assumed that 1% of companies are manufacturing the substance as the substance is manufactured in the 1 000 - 10 000 tonnes per year in the EU with two REACH registrants. Closed systems are also employed and measured exposure data is low for this sector.

Manufacture of pesticides and other agrochemical products

For calculating the number of exposed workers in this sector, it has been assumed that 10% of enterprises in C20.2 may be using the substance with 10% of these workers exposed. The substance is used in biocide products; although there is little publically available information on its use for this application. The use of the substance for biocide applications is only included as a consumer use in its REACH dossier as a disinfectant and for pest control, ao an assumption of 10% of workers potentially being exposed has been derived.

Manufacture of soaps and detergents, cleaning and polishing preparations, perfumes and toilet preparations

In calculating the number of workers in this sector, due to the lack of available information, assumptions have been made. An assumption of 10% enterprises in C20.4 has been derived as it is used as a fragrance in a wide variety of industries.[578] An assumption of 10% of workers being potentially exposed in this sector has been derived. During manufacturing, closed systems will also be employed although some exposure may be possible. For this use, the substance has concentration limits for the final products (IFA guidelines has a highest concentration limit of 1.42%. For its REACH

[578] ECHA (2017): CLH report for 2-(4-tert-butylbenzyl)propionaldehyde. Dated December 13, 2017. Available at: https://echa.europa.eu/documents/10162/c4cf84f3-f8a1-33af-1a4c-fd278444547a

registration, there are two registrants/suppliers with a tonnage band of 1 000- 10 000 tonnes per annum.

Cleaning activities

This use has the highest number of potentially exposed workers. Due to the lack of available information, assumptions have been performed for deriving the number of exposed workers. An assumption of 50% of workers in Services in buildings and landscape activities has been used. It is assumed that 1% of these workers may be exposed from the use and concentration of the substance in cleaning products. Exposure may occur during its use, for example during roller application or brushing and non-industrial spraying as discussed in the registration dossier. The substance is used in cleaning products with uses in polishes and wax blends and washing and cleaning products. Safety data sheets indicate concentrations of up to 1% of the substance.[579]

Table X16-5: Exposed workforce by sector

Sector	Assumptions	Number of exposed workers of reproductive age
Manufacture of basic chemicals, fertilisers and nitrogen compounds, plastics and synthetic rubber in primary forms (C20.1)	• 1,243,800 workers of reproductive age in C20 • 30% of C20 enterprises are C20.1; • 1% of C20.1 are manufacturing the substance; • 5% of these workers are exposed	187 workers
Manufacture of pesticides and other agrochemical products (C20.2)	• 2% of C20 enterprises are C20.2; • 10% of C20.2 enterprises are using the substance; • 10% of these workers are exposed	249 workers
Manufacture of soaps and detergents, cleaning and polishing preparations, perfumes and toilet preparations (C20.4)	• 32% of C20 enterprises are C20.4 (299,648 workers); • 10% of C20.4 enterprises are using the substance; • 10% of these workers are exposed to the substance	3980 workers
Cleaning activities	• 3,422,000 workers in Services to buildings and landscape activities • 50% are involved in cleaning activities • 1% of these workers are exposed	17110
Source: Eurostat		

[579] Newell Rubbermaid (2015): Clean Sense MB3000 Safety Data Sheet. Available at: https://www.rv.is/library/Myndir/R0260041_sds_microburst_3000_clean_sense_en.pdf%20(R0260041)

X16.4.2 Breakdown by gender and age

Table X16-6: Exposed workforce by sector for males of reproductive age		
Sector	**Assumptions**	**Number of male workers/female workers of reproductive age**
Manufacture of basic chemicals, fertilisers and nitrogen compounds, plastics and synthetic rubber in primary forms (C20.1)	• 936,400 males of reproductive age and 307,400 females of reproductive age in manufacture of chemicals and chemical products; • 30% of C20 enterprises are C20.1; • 1% of C20.1 are manufacturing the substance; and • 5% of these workers are exposed	140/47
Manufacture of pesticides and other agrochemical products (C20.2)	• 936,400 males of reproductive age in manufacture of chemicals and chemical products; • 2% of C20 enterprises are C20.2; • 10% of C20.2 enterprises are using the substance; and • 10% of these workers are exposed	187/62
C20.4: Manufacture of soaps and detergents, cleaning and polishing preparations, perfumes and toilet preparations	• 936,400 males and 307,400 of reproductive age in manufacture of chemicals and chemical products; • 32% of C20 enterprises are C20.4 • 10% of C20.4 enterprises are using the substance; and • 10% of these workers are exposed to the substance	2996/1684
Cleaning activities	• 2,018,500 males of reproductive age and 1,043,500 female workers in Services to buildings and landscape activities; • 50% are involved in cleaning activities; and • 1% of these workers are exposed to the substance	10093/7017
Source: Eurostat		

X16.4.3 Exposed workers: conclusion

The number of potentially exposed workers to 2-(4-tert-butylbenzyl) propinoaldehyde is presented in the following table.

Table X16-7: Exposed workforce: conclusion			
Estimate	**No of exposed workers**	**Men of reproductive age**	**Women of reproductive age**
Estimate	21,526	13,416	8110
Estimate taken forward for modelling	21,526	13,416	8110
Alternative estimate for the sensitivity analysis	-	-	-
Annual rate of change taken forward for modelling	4%	4%	4%

X16.5 Exposure levels

X16.5.1 Exposure routes

Occupational exposure to 2-(4-tert-butylbenzyl)propinoaldehyde would mainly be through the dermal routes of exposure with inhalation considered to be of low relevance for occupational exposure.

Dermal exposure route

Exposure to the substance *via* the dermal route is expected in occupational settings. For a worker specific exposure scenario, the external dermal dose will not exceed 0.7 mg/kg bw/day, leading to a potential internal dose of 0.04 mg/kg bw/day (equivalent to 0.28 mg/m^3 inhaled exposure).[580] Using suitable gloves for the process categories results in a reduction of a factor of 10 for the external dermal dose.

Inhalation exposure route

Occupational exposure *via* the inhalation route is considered to be of low relevance. The substance has a low vapour pressure (0.25 Pa) and the scenarios of occupational use of the substance do not include the formation of aerosols:

- The inhalation exposure estimate has been calculated assuming 100% absorption via inhalation, a mean worker respiratory volume of 10 m^3 and a mean body weight of 70 kg.
- Exposure was calculated for a worst case scenario compared to realistic scenarios and further conservative assumptions re process conditions.
- The concentrations of TBP in air would not exceed 0.18 mg/m^3 as an air concentration 5 cm above the liquid surface. Considering a respiration volume of 10 m^3 during a shift and a mean body weight of 70 kg, a daily internal dose would result in 0.026 mg/kg bw for workers not wearing respiratory protection.

The calculated mean inhalation exposure estimates during an 8 hour shift does not exceed 0.22 mg/m^3, resulting in an internal dose of 0.03 mg/kg bw/day.

[580] Huntingdon Research Centre (1994); The Dermal Absorption of ^{14}C-Para-Tert-Butyl-AlphaMethylhydrocinnamaldehyde in Man. As cited in CLH report for 2-(4-tert-butylbenzyl) propionaldehyde. https://echa.europa.eu/documents/10162/2eff6c48-0950-4656-af10-342c574d5987

The external dermal dose in a worker specific exposure scenario does not exceed 0.7 mg/kg bw/day, leading to a potential internal dose of 0.04 mg/kg bw/day (equivalent to 0.28 mg/m^3 inhaled exposure).

X16.5.2 Current exposure levels

Dermal exposure levels

Dermal exposure levels have been calculated in the 2017 CLH report using ECETOC TRA or RISKOFDERM 2.1 which are presented in the following table.[581] The external dermal dose in a worker specific exposure scenario does not exceed 0.7 mg/kg bw/day, leading to a potential internal dose of 0.04 mg/kg bw/day (equivalent to 0.28 mg/m^3 inhaled exposure) stated in the CLH report.

Table X16-8: 2-(4-tert-butylbenzyl)propinoaldehyde – exposure concentrations

Activities	PROC code	Long term systemic dermal external (mg/kg bw/d)	Long term systemic dermal internal (mg/kg bw/d)[3]
Manufacture	2	0.1371	0.0096
	8b (vessels)	0.2114	0.0148
	8b (drums)	0.0000	0.0000
	15	0.0343	0.0024
Compounding	1	0.0034	0.0002
	3	0.0686	0.0048
	5 (automated)	0.0691	0.0048
	5 (manual)	0.0124	0.0009
	8a	0.3429	0.0240
	8b	0.4157	0.0291
	9	0.1714	0.0120
	15	0.0343	0.0024
Formulation	1	0.0009	0.0001
	3	0.0171	0.0012
	5	0.3429	0.0240
	8a	0.1371	0.0096
	8b	0.3429	0.0240
	9	0.0686	0.0048
	14	0.0343	0.0024
	15	0.0086	0.0006
Industrial cleaning	1	0.0003	0.00002
	2	0.0137	0.0010
	4	0.0686	0.0048
	7	0.4286	0.0300
	8b	0.1371	0.0096
	10	0.2743	0.0192
	13	0.1371	0.0096
Professional cleaning	1	0.0003	0.0000
	2	0.0137	0.0010
	4	0.0686	0.0048
	8a	0.1371	0.0096
	8b	0.1371	0.0096
	10	0.2743	0.0192
	11	0.1071	0.0075

[581] ECHA (2017): CLH report for 2-(4-tert-butylbenzyl)propionaldehyde. Dated December 13, 2017. Available at: https://echa.europa.eu/documents/10162/c4cf84f3-f8a1-33af-1a4c-fd278444547a

Table X16-8: 2-(4-tert-butylbenzyl)propinoaldehyde – exposure concentrations			
Activities	**PROC code**	**Long term systemic dermal external (mg/kg bw/d)**	**Long term systemic dermal internal (mg/kg bw/d)[3]**
	13	0.1371	0.0096
Source: ECHA (2017): CLH report for 2-(4-tert-butylbenzyl)propionaldehyde. Dated December 13, 2017. Available at: https://echa.europa.eu/documents/10162/c4cf84f3-f8a1-33af-1a4c-fd278444547a			

Inhalation exposure levels

The 2017 CLH report provides information about current exposure levels to 2-(4-tert-butylbenzyl) propinolaldehyde in occupational settings. Table X16-9 provides measured air exposure concentrations at BASF SE for a number of activities/operations. The measured concentrations for all the measurements are below the limit of detection (LOD).

Table X16-9: 2-(4-tert-butylbenzyl)propinoaldehyde – exposure concentrations		
Activities	**Detection limit (mg/m^3)**	**Measurement duration (mins)**
Laboratory	<0.001	250
Laboratory	<0.00098	240
Transfer of substance into drums	<0.00098	240
Transfer of substance into drums	<0.00098	240
Transfer of substance into drums	<0.00098	240
Drum filling and control activities in production facility	<0.001	500
Sampling and control activities in production facility	<0.001	500
Sampling and control activities in production facility	<0.001	500
Activities in production facility	<0.00098	240
Activities in production facility	<0.00098	240
Activities in production facility	<0.001	250
Activities in production facility	<0.001	250
Activities in production facility	<0.001	250
Source: ECHA (2017): CLH report for 2-(4-tert-butylbenzyl)propionaldehyde. Dated December 13, 2017. Available at: https://echa.europa.eu/documents/10162/c4cf84f3-f8a1-33af-1a4c-fd278444547a		

Inhalation exposure has also been calculated in the CLH report using ECETOC TRA or Stoffenmanager 5.1 and these are presented in the following table.

- The inhalation exposure estimate has been calculated assuming a 100% absorption via inhalation, a mean worker respiratory volume of 10 m^3 and a mean body weight of 70 kg.;
- Exposure was calculated for a worst-case scenario compared to realistic scenarios and further conservative assumptions for process conditions; and
- The concentrations of TBP in air would not exceed 0.18 mg/m^3 as an air concentration 5 cm above the liquid surface. Considering a respiration volume of 10 m^3 during a shift and a mean body weight of 70 kg, a daily internal dose would result in 0.026 mg/kg bw for workers not wearing respiratory protection.

The calculated mean inhalation exposure estimates during an 8-hour shift does not exceed 0.22 mg/m^3, resulting in an internal dose of 0.03 mg/kg bw/day.

Table X16-10: 2-(4-tert-butylbenzyl)propinoaldehyde – exposure concentrations			
Activities	**PROC code**	**Long term inhalation external (mg/m³)**	**Long term systemic inhalation internal (mg/kg bw/d)²**
Manufacture	2	0.0097	0.0014
	8b (vessels)	0.0201	0.0029
	8b (drums)	0.0091	0.0013
	15	0.0201	0.0029
Compounding	1	0.0170	0.0024
	3	0.0021	0.0003
	5 (automated)	0.0097	0.0014
	5 (manual)	0.0446	0.0064
	8a	0.0393	0.0056
	8b	0.0101	0.0014
	9	0.2128	0.0304
	15	0.0115	0.0016
Formulation	1	0.0043	0.0006
	3	0.0039	0.0006
	5	0.0395	0.0056
	8a	0.0047	0.0007
	8b	0.0408	0.0058
	9	0.0851	0.0122
	14	0.4256	0.0608
	15	0.0102	0.0015
Industrial cleaning	1	0.0009	0.0001
	2	0.0851	0.0122
	4	0.2979	0.0426
	7	0.1061	0.0152
	8b	0.0851	0.0122
	10	0.0950	0.0136
	13	0.0851	0.0122
Professional cleaning	1	0.0009	0.0001
	2	0.2979	0.0426
	4	0.2913	0.0416
	8a	0.2979	0.0426
	8b	0.1703	0.0243
	10	0.2913	0.0416
	11	0.2581	0.0369
	13	0.1703	0.0243
Source: ECHA (2017): CLH report for 2-(4-tert-butylbenzyl)propionaldehyde. Dated December 13, 2017. Available at: https://echa.europa.eu/documents/10162/c4cf84f3-f8a1-33af-1a4c-fd278444547a			

Combined internal exposure

The combined internal exposure (dermal and inhalation) has also been calculated and these are discussed in the following table.

Table X16-11: 2-(4-tert-butylbenzyl)propinoaldehyde – exposure concentrations		
Activities	**PROC code**	**Long term systemic combined internal (mg/kg bw/d)**
Manufacture	2	0.0110
	8b (vessels)	0.0177
	8b (drums)	0.0013
	15	0.0053

Table X16-11: 2-(4-tert-butylbenzyl)propinoaldehyde – exposure concentrations		
Activities	**PROC code**	**Long term systemic combined internal (mg/kg bw/d)**
Compounding	1	0.0027
	3	0.0051
	5 (automated)	0.0062
	5 (manual)	0.0072
	8a	0.0296
	8b	0.0305
	9	0.0424
	15	0.0040
Formulation	1	0.0007
	3	0.0018
	5	0.0296
	8a	0.0103
	8b	0.0298
	9	0.0170
	14	0.0632
	15	0.0021
Industrial cleaning	1	0.0001
	2	0.0131
	4	0.0474
	7	0.0452
	8b	0.0218
	10	0.0328
	13	0.0218
Professional cleaning	1	0.0001
	2	0.0435
	4	0.0464
	8a	0.0522
	8b	0.0339
	10	0.0608
	11	0.0444
	13	0.0339
Source: ECHA (2017): CLH report for 2-(4-tert-butylbenzyl)propionaldehyde. Dated December 13, 2017. Available at: https://echa.europa.eu/documents/10162/c4cf84f3-f8a1-33af-1a4c-fd278444547a		

X16.5.3 Trends

There is no information available on exposure trends.

X16.6 Current Risk Management Measures (RMMs)

X16.6.1 Overview of RMMs

The REACH registration dossier recommends organisational measures, respiratory protection, eye protection and hand protection for exposure control. These are discussed in the following table. As discussed in section X16.5.1; dermal exposure is the most important route for occupational exposure this hand protection is essential (in the calculations in section X16.5.2: for all process categories, the use of suitable gloves as personal and product protective equipment has been included in the exposure assessment resulting in an additional reduction by a factor of 10 of the external dermal dose).

Table X16-12: 2-(4-tert-butylbenzyl)propionaldehyde REACH protective measures	
Measure	**Details**
Organisational measures	Avoid contact with skin, eyes and clothing. Closed work clothing is recommended and store work clothing separately. No eating, drinking, smoking or tobacco use at the place of work
Respiratory protection	If ventilation is inadequate, wear respiratory protection. Use gas filters for gases/vapours of organic compounds (for example EN 14387 type A)
Eye protection	Safety glasses with side-shields (such as EN 166)
Hand protection	Use chemical resistant gloves (EN 374); butyl rubber (0.7 mm coating thickness) and nitrile rubber (0.4 mm coating thickness)
Source: ECHA (2018): 2-(4-tert-butylbenzyl)propionaldehyde REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/13572/9	

The safety data sheet for the substance, also additionally recommends the following measures:[582]

- Engineering measures: Wash hands before breaks and at the end of the work day and handle in accordance with good industrial hygiene and safety practice;
- Body protection: Complete suit protection against chemicals; and
- Respiratory protection: Where the risk assessment shows that the use of air-purifying respirators are recommended, then use a full-face respirator with type ABEK (EN 14387) respiratory cartridges as a backup to engineering controls. It is also recommended to use a full-face respirator if no engineering controls are available.

Closed systems are also used for handling the substance, with the following PROC codes used:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions; and
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions

The filling of drums (PROC 8b) is a fully automated process, so dermal exposure is not expected.[583]

X16.6.2 Best/good practice examples

No examples of best/good practice for this substance have so far been identified.

[582] Sigma Aldrich (2015): 2-(4-tert-Butylbenzyl)propinoaldehyde Safety Data Sheet. Available at: https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=GB&language=en&productNumber=43884&brand=SIAL&PageToGoToURL=https%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Fsial%2F43884%3Flang%3Den

[583] ECHA (2017): CLH report for 2-(4-tert-butylbenzyl)propionaldehyde. Dated December 13, 2017. Available at: https://echa.europa.eu/documents/10162/c4cf84f3-f8a1-33af-1a4c-fd278444547a

X16.6.3 Voluntary industry initiatives

There is no specific information concerning voluntary industry initiatives for 2-(4-tert-butylbenzyl)propinoladehyde. BASF, who are one of the REACH registrants and manufacture the substance have a Product Stewardship Program.[584] This program includes:

- By 2020, review all risk assessments for substances that are sold in quantities larger than one ton per year;
- Global product database with safety data sheets; and
- Training on handling, for example chloroformates.

The International Fragrance Association (IFRA) also has IFRA standards for the use of fragrance ingredients. These standards are based on risk assessments performed by external experts and are part of the IFRA Code of Practice.[585] 2-(4-tert-butylbenzyl)propinolaldehyde is on the standards list under p-tert-Butyl-alpha-methylhydrocinnamic aldehyde (p-BMHCA, Lilestralis, Lilial, Lysmeral) and is a restricted substance.[586] Under the IFRA standards, the concentration permitted of the substance in eleven product categories is limited from 0.12% to a maximum of 5% for one of the product categories.[587]

X16.6.4 Other restrictions

IFRA have proposed the following concentration limits for the substance in products:

- Hydroalcoholic-based fragrances (such as aftershave, cologne, perfume, Eau de Toilette) with a concentration limit of 1.42%;
- Deodorants: concentration limit of 0.09%;
- Make up product: concentration limit of 0.04%;
- Face cream: concentration limit of 0.05%;
- Hand cream: concentration limit of 0.05%;
- Body lotion: concentration limit of 0.06%; and
- Hair styling: concentration limit of 0.04%

X16.7 Market analysis

The general characteristics of the sectors with companies in which exposure can occur are summarised below. These sectors are:

- C20.1 Manufacture of basic chemicals, fertilisers and nitrogen compounds, plastics and synthetic rubber in primary forms
- C20.2 Manufacture of pesticides and other agrochemical products

[584] BASF SE (2018): Product Stewardship Worldwide. Available at: https://www.basf.com/en/company/sustainability/management-and-instruments/responsible-care/product-stewardship-and-global-product-strategy/product-stewardship-worldwide.html

[585] IFRA (2007): About the Standards. Available at: http://www.ifraorg.org/en-us/about-the-standards#.W2LuJMInaUl

[586] IFRA (2007): Index of IFRA Standards- 48th Amendment. Available at: http://www.ifraorg.org/en-us/search/s/lysmeral#.W2Lu8cInaUk

[587] IFRA (2015): p-tert-Butyl-alpha-methylhydrocinnamic aldehyde (p-BMHCA) IFRA standard. Available at: http://www.ifraorg.org/en-us/search/s/lysmeral#.W2Lu8cInaUk

- C20.4: Manufacture of soaps and detergents, cleaning and polishing preparations, perfumes and toilet preparations
- Cleaning activities: n/a on Eurostat

X16.7.1 Number of SMEs in each sector

Table X16-13: Number and proportion of SMEs by size of enterprise and sector									
Sector	TOTAL	Micro		Small		Medium		Large	
	No. firms	No. firms	% of total	No. firms	% of total	No. firms	% of total	No. firms	% of total
C20.1	**8,980**	5,190	58%	2,010	22%	980	11%	360	4%
C20.2	**630**	360	57%	140	22%	100	16%	20	3%
C20.4	**9,560**	7,090	74%	1,600	17%	680	7%	170	2%
Source: Eurostat's Structural Business Statistics database									

X16.7.2 Average turnover by size of enterprise

Table X16-14: Average turnover by sector and size of enterprise, 2016												
Sector	Micro			Small			Medium			Large		
	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m
C20.1	6,854	5,190	1.32	19,422	2,010	9.66	68,909	980	70.32	234,358	360	650.99
C20.2	194	360	0.54	852	140	6.09	4,697	100	46.97	5,005	20	250.25
C20.4	2,315	7,090	0.33	5,848	1,600	3.66	17,418	680	25.61	47,164	170	277.44
Source: Eurostat's Structural Business Statistics database												

X16.7.3 R&D expenditure

Table X16-15: Business expenditure on R&D per sector (in € million), EU28		
Sector	Data availability	R&D expenditure (in €m)
C20.1	C20	6,659.7
C20.2	C20	6,659.7
C20.4	C20	6,659.7
Source: Eurostat Notes: EU28 totals do not include data for some member states, due to confidentiality.		

X16.8 Burden of ill health

X16.8.1 Cases of ill health

To assess the potential cases of ill health, two exposure scenarios have been considered:

- Highest value from exposure data: 0.2979 mg/m^3; and
- 100 x DNEL (inhalation): 44 mg/m^3

As there are no OELs for this substance, this scenario has not been considered.

Highest value from exposure data

The highest value from exposure data (0.2979 mg/m^3) is below the lowest threshold for effect (17.5 mg/m^3- see Table X16-16), so there would be no fertility or developmental effects at this level.

100x DNEL scenario

A number of endpoints have been found to have a threshold for effect that lies at 100x DNEL (44 mg/m^3) and these are discussed in the following table.

Table X16-16: Effects at 100 x DNEL

Monetisable effect	Effect	Threshold	DRR	Value
Impaired fertility-male	Reduction in mean fraction of motile sperm in the cauda epididymis	17.5	y=-1.71x+29.925	-45.3
	Increase in mean fraction of abnormal sperm	17.5	y= 1.9x-33.25	50.4
	Reduction in mean sperm head count in the cauda epididymis	17.5	y=-0.87x+15.225	-23.1
	Testicular atrophy	43.8	y=0.75x-32.85	0.2
	Testicular atrophy	8.75	y=1x-8.75	35.3
Impaired fertility-female	Reduction in mean implantation sites	17.5	y=-1.74+30.45	-46.1
	Reduction in mean pups delivered	17.5	y=-1.83+32.025	-48.5
Impaired fertility-female (can only measure males)	Decrease in mean number of implantation sites (P1)	5.25	y= -1.13+5.9325	-43.8
Spontaneous abortion	Increase in mean post-implantation losses (mean resorptions)	22.2	y= 4.96+110.112	108.1

For these effects, only the increase in mean fraction of abnormal sperm (impaired fertility-male) has been used for calculating the number of potential cases. The other possible effects have not been able to be modelled as:

- For the first three effects for impaired fertility-male; only one is required to be estimated and the effect with the highest value has been used;
- Testicular atrophy has not been used due to the high dosage used;

- For reduction in mean implantation sites, the study design means that it is unable distinguish between effect in male &/or female parents and this effect also cannot be correlated to humans;
- For mean pups delivered, in this study there was maternal toxicity and the effect cannot be correlated to humans;
- The decrease in mean number of implantation sites (impaired fertility- female) can only be measured for males; and
- For increase in mean post-implantation losses this cannot be correlated to humans.

Number of cases

The endpoint that has been used to estimate is increase in mean fraction of abnormal sperm (impaired fertility- male). The number of male exposed workers used is 13,416 workers in the calculation

The endpoint that has been found to have a threshold that can be modelled is discussed in the following table. For calculating the number of the cases, the following has been used as discussed below. The value used for the workforce with abnormal sperm is the lower reference value which has been generated by WHO for abnormal sperm

- A value of 2.5% has been used for the workforce with abnormal sperm;[588] and
- A value of 9.8% has been used for mean percentage of abnormal sperms[589]

Table X16-17: 2-(4-tert-butylbenzyl) propionaldehyde – effects used for estimation					
Monetisable effect	**Effect**	**Threshold**	**DRR**	**Value**	**Cases**
Impaired fertility- male	Increase in mean fraction of abnormal sperm	17.5	y= 1.9x-33.25	50.4	17

[588] Cooper TG et al (2010): World Health Organisation reference values for human semen characteristics. Human Reproductive Update, 16(3), pp 231-245.

[589] ECHA (2018): REACH dossier for 2-(4-tert-butylbenzyl) propionaldehyde. Unnamed report, 2017a. Available at:https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/13572/7/9/2/?documentUUID=5e8708fc-7064-4a26-935d-76ae118c4448

Annex 17 Dodecyl Phenols

X17.1 Introduction

X17.1.1 Relevant substance(s)

There are 6 shortlisted substances in the Dodecyl phenols group and these are set out in Table X17-1 below.

Table X17-1: Focal substances in the Dodecylphenols group			
EC Number	**CAS Number**	**Name**	**Alternative names**
310-154-3	121158-58-5	Phenol, dodecyl-, branched	*Trade Names* Dodecylphenol T Dodecylphenol, mixed isomers (CAS No. 27193-86-8) Phenol, (tetrapropenyl), derivatives (CAS No. 74499-35-7) Phenol, 4-dodecyl, branched (CAS No. 210555-94-5) Phenol, tetrapropylene (CAS No. 57427-55-1) Tetrapropenyl phenol *IUPAC Names* 4-(3,4,5-trimethylheptyl)phenol 4-dodecyl phenol Phenol, alkyl branched (species comprising decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, substituents) Phenol, para alkylation products with C12-rich branched olefins from propene oligomerisation Tetrapropenyl phenol
259-048-8	54261-67-5	Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate)	*IUPAC Names* Zinc bis[O,O-bis(4-dodecylphenyl) dithiophosphate] Zinc, bis[O,O-bis(dodecylphenyl) phosphorodithioato-.kappa.S,.kappa.S']-
272-233-8	68784-25-8	Phenol, dodecyl-, sulfurized, carbonates, calcium salts	*IUPAC Names* 4-(3,4,5-trimethylheptyl)phenol
272-234-3	68784-26-9	Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased	*Trade Names* Calcium alkylphenolate OLOA 219 OLOA 219C *IUPAC Names* Calcium phenate Overbased calcium phenate Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased containing Distillates (petroleum), hydrotreated heavy paraffinic (UVCB). Phenol, paraalkylation products with
272-486-4	68855-45-8	Phenol, dodecyl-, sulfurized, calcium salts	*IUPAC Names* Calcium phenate

Table X17-1: Focal substances in the Dodecylphenols group			
EC Number	**CAS Number**	**Name**	**Alternative names**
			Phenol, para-alkylation products with C10-15 branched olefins (C12 rich) derived from propene oligomerization, calcium salts, sulfurized, including distillates (petroleum), heavy paraffinic C10-C50
306-115-5	96152-43-1	Phenol, dodecyl-, branched, sulfurized	*IUPAC Names* Phenol, alkylation products with C10-15 branched olefins derived from propene oligomerisation, reaction products with sulfur monochloride, decene treated

There is read-across for Phenol, dodecyl-, branched, sulfurized to Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased and consequently, the same data is used throughout this section for both substances. Similarly, the same data is used for Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate) as for Phenol, dodecyl-, branched. Here, the read-across is not based as is usual on structural similarity but on the fact dodecyl phenol branched is a major contaminant/constituent of this mixture. Finally, there is no registration dossier for Phenol, dodecyl-, sulfurized, carbonates, calcium salts and it has not been possible to provide data for this substance. The following table summarises the read-across between substances and available data.

Table X17-2: Read-across for Dodecyl phenol substances	
Substance	**Reads across to…**
Phenol, dodecyl-, branched	Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate)
Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased	Phenol, dodecyl-, branched, sulfurized
Phenol, dodecyl-, sulfurized, calcium salts	-
Phenol, dodecyl-, sulfurized, carbonates, calcium salts	N/A (No registration dossier available)

The figures below provide the chemical structures for the substances where registration dossiers are available.

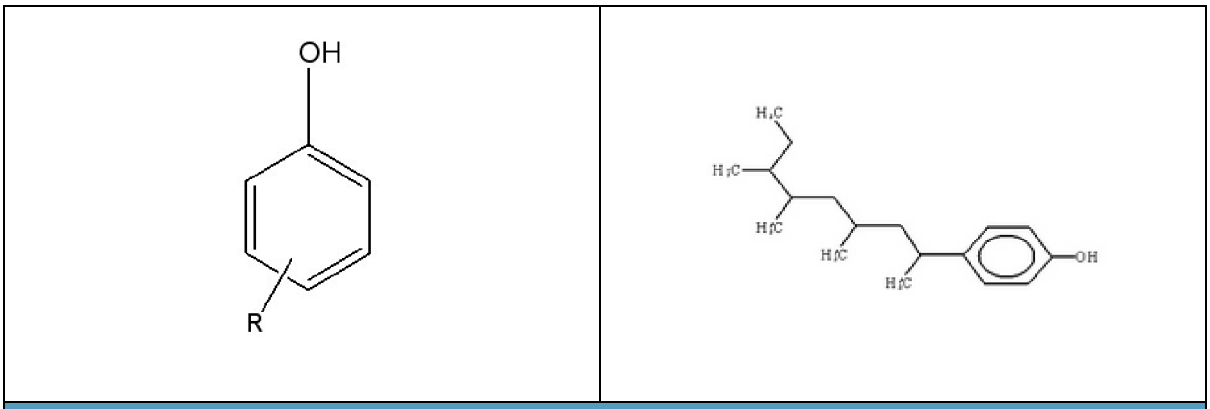


Figure X17-1: Phenol, dodecyl-, branched
Note: 2 separate registration dossiers exist, with the diagram on the left provided in the full registration under a joint submission, and the one on the right for an individual submission for intermediate use only.
https://echa.europa.eu/registration-dossier/-/registered-dossier/14705
https://echa.europa.eu/registration-dossier/-/registered-dossier/1533

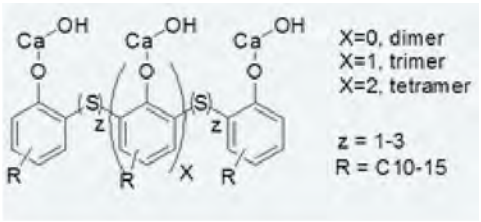


Figure X17-2: Phenol, dodecyl-, sulfurized, calcium salts
https://echa.europa.eu/registration-dossier/-/registered-dossier/13858

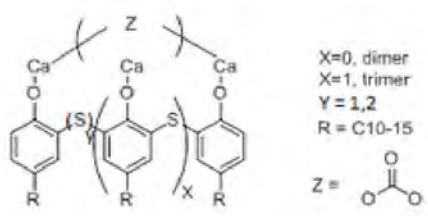


Figure X17-3: Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased
https://echa.europa.eu/registration-dossier/-/registered-dossier/15042

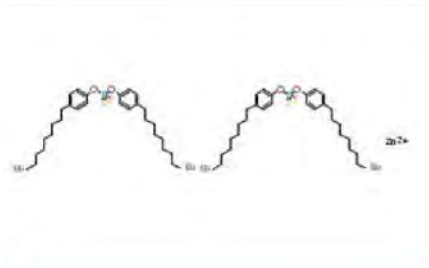


Figure X17-4: Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate)
https://echa.europa.eu/registration-dossier/-/registered-dossier/12713

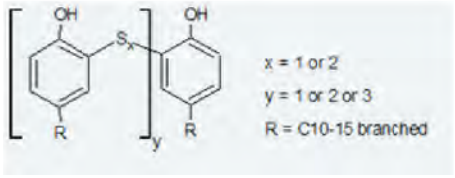


Figure X17-5: Phenol, dodecyl-, branched, sulfurized
https://echa.europa.eu/registration-dossier/-/registered-dossier/2225

X17.1.2 Hazard classification(s)

Hazard classifications for the dodecyl phenols are presented in A16-2 below.

Table X17-3: Hazard classifications for Dodecylphenols			
Substance	**Repr. 1A/1B/2**	**Hazard classification**	**Description**
Phenol, dodecyl-, branched[590]	Repr. 1B Repr. 2 Aquatic Chronic 1 Aquatic Acute 1 Eye Dam. 1 Skin Corr. 1C Skin Irrit. 2 Skin Corr. 1A Skin Corr. 1B Acute Tox. 4	H360F H361 H410 H400 H318 H314 H319 H314 H314 H302	May damage fertility Suspected of damaging fertility or the unborn child Very toxic to aquatic life with long lasting effects Very toxic to aquatic life Causes serious eye damage Causes severe skin burns and eye damage Causes serious eye irritation Causes severe skin burns and eye damage Causes severe skin burns and eye damage Harmful if swallowed
Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate)[591]	Repr. 1B Repr. 2 Aquatic Chronic 3 Aquatic Chronic 2	H360 H361 H412 H411	May damage fertility or the unborn child. Suspected of damaging fertility or the unborn child Harmful to aquatic life with long lasting effects Toxic to aquatic life with long lasting effects
Phenol, dodecyl-, sulfurized, carbonates, calcium salts[592]	Repr. 1B Repr. 2 Aquatic Chronic 4 Eye Irrit. 2	H360 H361 H413 H319	May damage fertility or the unborn child Suspected of damaging fertility or the unborn child May cause long-lasting harmful effects to aquatic life Causes serious eye irritation
Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased[593]	Repr. 1B Repr. 2 Aquatic Chronic 3 Aquatic Chronic 4	H360 H361 H412 H413	May damage fertility or the unborn child Suspected of damaging fertility or the unborn child Harmful to aquatic life with long lasting effects May cause long-lasting harmful effects to aquatic life
Phenol, dodecyl-, sulfurized, calcium salts[594]	Repr. 1B Repr. 2 Aquatic Chronic 4 Eye Irrit. 2	H360 H361 H413 H319	May damage fertility or the unborn child Suspected of damaging fertility or the unborn child May cause long-lasting harmful effects to aquatic life Causes serious eye irritation
Phenol, dodecyl-, branched, sulfurized[595]	Repr. 1B Repr. 2 Aquatic Chronic 4	H360 H361 H413	May damage fertility or the unborn child Suspected of damaging fertility or the unborn child May cause long-lasting harmful effects to aquatic life

[590] https://echa.europa.eu/brief-profile/-/briefprofile/100.100.072
[591] https://echa.europa.eu/brief-profile/-/briefprofile/100.053.663
[592] https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/107496
[593] https://echa.europa.eu/brief-profile/-/briefprofile/100.065.878
[594] https://echa.europa.eu/brief-profile/-/briefprofile/100.065.878
[595] https://echa.europa.eu/brief-profile/-/briefprofile/100.096.421

X17.1.3 Existing OELs and BLVs

The literature review has not revealed any OELs (binding or indicative) for any of the six dodecyl phenol substances. However, DNELs were identified from REACH registrations and these are presented in Table X17-4 below.

Table X17-4: Occupational long-term and short-term DNELs via inhalation route for Dodecyl phenols		
Substance	**Long-term DNEL (mg/m³)**	**Short-term DNEL (mg/m³)**
Phenol, dodecyl-, branched	1.762	44.18
Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate)	7.3	1056
Phenol, dodecyl-, sulfurized, carbonates, calcium salts	3.5	
Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased	3.5	133.6
Phenol, dodecyl-,sulfurized, calcium salts	3.5	
Phenol, dodecyl-,branched, sulfurized	3.526	66.8

DNELs via the dermal route for substances where these have been identified are:

- 0.25 mg/kg bw/day (166 mg/kg bw/day) for Phenol, dodecyl-, branched
- 1.65 mg/kg bw/day (512 mg/kg bw/day short-term) for Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate)
- 0.5 mg/kg bw/day (80 mg/kg bw/day short-term) for Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased
- 3.12 mg/kg bw/day (80 mg/kg bw/day short-term) for Phenol, dodecyl-,branched, sulfurized

X17.1.4 Legislation other than CAD

None of the dodecyl phenols are on the Candidate List, the Authorisation List or the Restrictions List. However, Phenol, dodecyl-, branched is currently being evaluated under the CoRAP[596] and Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased was included in the CoRAP for substance evaluation to be evaluated in 2013 for concerns relating to human health/CMR, exposure/wide dispersive use, consumer use, and aggregated tonnage. The decision[597] on substance evaluation issued in October 2015 required registrants to submit additional and revised information on dermal and inhalation exposure, but it is noted that the decision was not addressed to i) Registrants who exclusively use the above substance as an on-site isolated intermediate and under strictly controlled conditions and ii) Registrants who cease manufacture/import.

Other EU legislation of potential relevance to the dodecyl phenols groups are illustrated in Table X17-5.

[596] Justification Document for the Selection of a CoRAP Substance, Federal Institute for Occupational Safety and Health, Germany 21/03/2017, available at: https://echa.europa.eu/documents/10162/13628/corap_justification_310-154-3_de_4703_en.pdf/af93486c-a7f7-58ec-2c35-57eeb3e372f1

[597] Available at: https://echa.europa.eu/documents/10162/ddf9f332-1d34-4762-a90a-00a15deef2de

Table X17-5: Additional EU regulation of relevance to dodecyl phenols		
Substance	**EU Regulation**	**Relevance**
Phenol, dodecyl-, branched	EU. REACH. Community Rolling Action Plan (CoRAP) Substances List (ECHA, 20 March 2018)	Year of planned evaluation: 2018 Evaluation by member state: DE Initial grounds for concern: Potential endocrine disruptor
Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate)	Council of Europe. Resolution AP (92) 2 on control of aids to polymerization in plastics coming into contact with food, Table 2.2, Migration limits (19 Oct 1992)	Plastic materials and articles prepared using aids to polymerization should not release their constituents to any of the simulants referred to in the migration testing provisions of EU Directives 82/711/EEC and 85/572/EEC in excess of 60 mg/kg or 10mg/dm2 of total migrants (overall migration limit). Metals should be determined only in 3% aqueous acetic acid, which is the most vigorous extractant among the food simulants specified in Directive 82/711/EEC, and in which the metals can be determined at the required limits. Migration Limit for this substance is 60mg/kg.
Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased	EU. REACH. Community Rolling Action Plan (CoRAP) Substances List (ECHA, 20 March 2018)	Year of planned evaluation: 2013 Evaluation by member state: NL Initial grounds for concern: Human health/CMR, Exposure/Wide dispersive use, Consumer use, Aggregated tonnage
Phenol, dodecyl-, sulfurized, calcium salts	EU. REACH. Community Rolling Action Plan (CoRAP) Substances List (ECHA, 20 March 2018)	Year of planned evaluation: 2016 Evaluation by member state: FR Initial grounds for concern: CMR, suspected PBT, wide dispersive use, consumer use, high (aggregated) tonnage

Table X17-6: Additional Member State Regulation of relevance to dodecyl phenols		
Substance	**Member State**	**Regulation**
Phenol, dodecyl-, branched	Sweden	Sweden. PRIO Guide to Chemical Substances of High Concern, as revised 28 June 2011 – Priority risk reduction substance. Because of the hazardous properties of the substance, it is particularly important to consider how the substance is handled and assess the risks for the intended use, consider substitution. Some of these substances are prohibited/restricted in Sweden. Also, potential PBT/vPvB. Identified as substance on which insufficient data are available to assess whether they fulfil the criteria for being PBT/vPvB substances.

X17.2 Summary of health endpoints, thresholds & DRRs

X17.2.1 Relevant health endpoints

The reproductive effects of exposure to dodecyl phenols identified through literature review are summarised below. The table below only lists adverse effects which have been deemed as potentially relevant to humans (i.e. they have a potential for human effects correlation), a no-effect threshold and a Dose-Response Relationship (DRR) could be derived and the source of the data is not a study that is clearly irrelevant to occupational exposure.

Table X17-7: Dodecyl phenols – summary of health effects			
Health effect identified in literature	Fertility/ development?		Monetisable effect correlate
	Fer	Dev	
Phenol, dodecyl-, branched			
Increased incidence of ovaries with decreased presence of corpora lutea (5 or less) (F1)	Fer	Dev	Impaired fertility – male offspring*
Increased incidence of ovaries with decreased presence of corpora lutea (5 or less) (F0)	Fer		Impaired fertility – female
Decreased epididymis sperm concentration(F0)	Fer		Impaired fertility – male
Decreased vaginal patency (F1 females)	Fer	Dev	Impaired fertility – male offspring*
Increased oestrous cycle length (F0)	Fer		Impaired fertility – female
Increased oestrous cycle length (F1)	Fer	Dev	Impaired fertility – male offspring*
Fertility index decreased	Fer		Impaired fertility – female Impaired fertility – male
Copulation index decreased	Fer		Impaired fertility – female Impaired fertility – male
Decrease in the ages of the first occurrence of oestrus	Fer	Dev	No monetisable effect correlate
Decreased number of implantation sites (F0)	Fer		Impaired fertility – female
Decreased number of pups born (F2a)	Fer	Dev	Impaired fertility – male offspring*
Decreased live litter size (F2a)	Fer	Dev	Impaired fertility – male offspring*
Decreased pup body weight-male-PND 7 (F1)		Dev	No monetisable effect correlate
Decreased pup body weight-female-PND 7 (F1)		Dev	No monetisable effect correlate
Decreased pup body weight-female-PND 21 (F1)		Dev	No monetisable effect correlate
Increased incidence of skeletal malformations involving a curved scapula and/or abnormally shaped long bones		Dev	No monetisable effect correlate
Phenol, dodecyl-, sulfurized, calcium salts			
Increased number of dead pups at on lactation day 0 (F1 pups)	Fer		Spontaneous abortion/still-birth
Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased			
Pre-implantation loss	Fer		Impaired fertility – female
Notes: Fertility effects on F1 are treated as 'developmental' in this table. All effects observed in multiple generations assigned to the earliest generation, e.g. F2 effects assigned to F1 for monetisation purposes, using the probabilities for F2 as the worst-case scenario. Effects observed in F1 assigned to both F0 and F1, using the F1 probabilities for both F0 and F1 as the worst case scenario. *Only male offspring fertility monetary value has been identified and all cases of F1 infertility are therefore valued as male infertility.			

Other health endpoints

Other potentially relevant but non-reprotoxic health effects arising from exposure to dodecyl phenols identified from the hazard classifications and literature review include:

Phenol, dodecyl-, branched

- Serious eye damage,
- Serious skin burns
- Harmful if swallowed

Phenol, dodecyl-, sulfurized, carbonates, calcium salts

- Causes serious eye irritation

It is noted from above that all six substances may have harmful effects on aquatic life in addition to reprotoxic and these other health effects identified above.

X17.2.2 Summary of thresholds and DRRs

The no effect thresholds (inhalation 8-hr TWA mg/m3) and effect slopes, together with the maximum air exposure concentrations (8-hr TWA mg/m3) for which the effect slopes are valid, are summarised below. For an overview of how these values were derived, refer to Annex 1.

Table X17-8: Dodecyl phenols – effects, thresholds and DRRs

Health effect	Threshold (mg/m^3)	Slope (% effect change/ mg/m^3)	Maximum range of slope applicability (mg/m^3)	Monetisable effect correlate
Phenol, dodecyl-, branched				
Increased incidence of ovaries with decreased presence of corpora lutea (5 or less) (F1)	26.25	1.84	131.25	Impaired fertility – male offspring*
Increased incidence of ovaries with decreased presence of corpora lutea (5 or less) (F0)	26.25	0.17	131.25	Impaired fertility – female
Decreased epididymis sperm concentration(F0)	26.25	-0.20	131.25	Impaired fertility – male
Decreased vaginal patency (F1 females)	26.25	-0.15	131.25	Impaired fertility – male offspring*
Increased oestrous cycle length (F0)	26.25	0.24	131.25	Impaired fertility – female
Increased oestrous cycle length (F1)	26.25	0.49	131.25	Impaired fertility – male offspring*
Fertility index decreased	43.75	-0.46	218.75	Impaired fertility – female Impaired fertility – male
Copulation index decreased	43.75	-0.45	218.75	Impaired fertility – female Impaired fertility – male
Decrease in the ages of the first occurrence of oestrus	87.5	-0.03	350	No monetisable effect correlate
Decreased number of implantation sites (F0)	26.25	-0.11	131.25	Impaired fertility – female
Decreased number of pups born (F2a)	26.25	-0.23	131.25	Impaired fertility – male offspring*

Table X17-8: Dodecyl phenols – effects, thresholds and DRRs				
Health effect	**Threshold (mg/m^3)**	**Slope (% effect change/ mg/m^3)**	**Maximum range of slope applicability (mg/m^3)**	**Monetisable effect correlate**
Decreased live litter size (F2a)	26.25	-0.28	131.25	Impaired fertility – male offspring*
Decreased pup body weight-male-PND 7 (F1)	2.62	-0.36	26.22	No monetisable effect correlate
Decreased pup body weight-female-PND 7 (F1)	2.62	-0.35	26.22	No monetisable effect correlate
Decreased pup body weight-female-PND 21 (F1)	2.62	-0.37	26.22	No monetisable effect correlate
Increased incidence of skeletal malformations involving a curved scapula and/or abnormally shaped long bones	175	0.03	525	Skeletal abnormalities of the limbs
Phenol, dodecyl-, sulfurized, calcium salts				
Increased number of dead pups at on lactation day 0 (F1 pups)	525	0.01	1750	Spontaneous abortion/still-birth
Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased				
Pre-implantation loss	350	0.02	1750	Impaired fertility – female

X17.3 Relevant sectors, uses, and operations

This section provides an overview of the relevant sectors, uses and activities in which occupational exposure to the dodecyl phenol substances can be expected to occur.

According to substance information provided on the ECHA website[598], Phenol, dodecyl-, branched is primarily used as a monomer for polymer production and is used in the manufacturing of chemicals.

The justification document developed by the German Federal Institute for Occupational Safety and Health for including the substance in the CoRAP identified information included in the ECHA dissemination site which states that dodecyl, phenol branched is used as an intermediate for the manufacture of chemicals, rubber products and plastic products. An earlier risk evaluation report provided by UK in 2007 also identified its use for the production of oil and lubricant additives and additives may contain a significant amount of unreacted alkylphenol and which are used in petrol and diesel powered road vehicles and marine diesel engines. This latter aspect led to the conclusion that a wide dispersive use can be assumed.[599]

[598] https://echa.europa.eu/substance-information/-/substanceinfo/100.100.072, https://echa.europa.eu/registration-dossier/-/registered-dossier/14705

[599] Justification Document for the Selection of a CoRAP Substance, Federal Institute for Occupational Safety and Health, Germany 21/03/2017, available at: https://echa.europa.eu/documents/10162/13628/corap_justification_310-154-3_de_4703_en.pdf/af93486c-a7f7-58ec-2c35-57eeb3e372f1

It is, however, noted that the evaluation for inclusion in the CoRAP was initiated as a result of the substance's potential as an endocrine disruptor and exposure of workers was not highlighted under the initial grounds for concern (exposure/risk based concerns).

All of the other 5 dodecyl phenols are identified as being used in lubricants, greases and hydraulic fluids. Table X17-9 below sets out the uses identified against their respective NACE Codes.

Table X17-9: Uses identified for dodecyl phenols			
Substance	**Relevant uses**	**Relevant sectors**	**Links**
Phenol, dodecyl-, branched	Used as a monomer for polymer production; used in manufacturing of chemicals	C20: Manufacture of chemicals and chemical products C22: Manufacture of plastic and rubber products	https://echa.europa.eu/substance-information/-/substanceinfo/100.100.072 https://echa.europa.eu/registration-dossier/-/registered-dossier/14705
Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate)	Used in lubricants, greases and hydraulic fluids	C29: Manufacture of motor vehicles, trailers and semi-trailers G: Wholesale and Retail Trade; Repair of Motor Vehicles and Motorcycles	https://echa.europa.eu/substance-information/-/substanceinfo/100.053.663 https://pubchem.ncbi.nlm.nih.gov/compound/23363560#section=Use-and-Manufacturing
Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased	Used in lubricants, greases and hydraulic fluids	C29: Manufacture of motor vehicles, trailers and semi-trailers G: Wholesale and Retail Trade; Repair of Motor Vehicles and Motorcycles	https://echa.europa.eu/substance-information/-/substanceinfo/100.065.648
Phenol, dodecyl-, sulfurized, carbonates, calcium salts	Used in lubricants, greases and hydraulic fluids	C29: Manufacture of motor vehicles, trailers and semi-trailers G: Wholesale and Retail Trade; Repair of Motor Vehicles and Motorcycles	https://echa.europa.eu/substance-information/-/substanceinfo/100.065.647
Phenol, dodecyl-, sulfurized, calcium salts	Used in lubricants, greases and hydraulic fluids	C29: Manufacture of motor vehicles, trailers and semi-trailers G: Wholesale and Retail Trade; Repair of Motor Vehicles and Motorcycles	https://echa.europa.eu/registration-dossier/-/registered-dossier/13858
Phenol, dodecyl-, branched, sulfurized	Used in lubricants and greases	C29: Manufacture of motor vehicles, trailers and semi-trailers G: Wholesale and Retail Trade; Repair of Motor Vehicles and Motorcycles	https://echa.europa.eu/substance-information/-/substanceinfo/100.096.421

Information from consultation

None of the company respondents to the consultation indicated that they were using any of the dodecyl phenols.

2 industry associations indicated that workers in their member companies were exposed to dodecyl phenols (one association did not indicate the specific substance and the other specified Phenol,

dodecyl-, branched) and one of these associations indicated that their members were involved in cable production and installation under the following NACE codes:

- NACE2731, Manufacture of fibre optic cables
- NACE2732, Manufacture of other electronic and electric cables and wires

X17.3.1 Nature of exposure

Phenol, dodecyl-, branched has the following PROC codes:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 4: Chemical production where opportunity for exposure arises;
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities; and
- PROC 15: Use as laboratory reagent

Phenol, dodecyl-sulfurized, carbonates, calcium salts has the following PROC codes:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 4: Chemical production where opportunity for exposure arises;
- PROC 5: Mixing or blending in batch processes;
- PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities;
- PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing);
- PROC 15: Use as laboratory reagent; and
- PROC 20: Use of functional fluids in small devices

Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate) has the following PROC codes:

PROC 1, PROC 2, PROC 3, PROC 4, PROC 5, PROC 7, PROC 8a, PROC 8b, PROC 9, PROC 10, PROC 11, PROC 13, PROC 15 and PROC 20. PROCs 4, 5, 7, 8a, 8b, 9, 10, 11, 13, 15 and 20 would likely involve the potential of exposure.

Phenol, dodecyl-, sulfurized, carbonates, calcium salts is only pre-registered under REACH, so no risk management measures are available from REACH.

X17.4 Exposed workforce

Occupational and consumer exposures to dodecyl phenols are expected to be very low based on the compounds' physicochemical properties, use and handling patterns. Dodecyl phenols are used as a chemical intermediate and raw material in the production of other chemical products. It does not have direct applications as a finished material and is not an intended component of any consumer product. Potential releases of dodecyl phenols to the environment may occur during production, use as a lubricant additive, blending lubricant additives into finished oils and use and disposal of used lubricants

X17.4.1 Total number of exposed workers

No information on the number of workers potentially or actually exposed to dodecyl phenols has been identified from literature and internet searches.

The table below identifies the number of workers of reproductive age (women workers aged 15-49 and male workers aged 15+) working in the different sectors where the substances are used in 2017.

Table X17-10: Dodecyl phenols – Total number of M and F workers in Sectors where used				
Sector	**Sub-sector/uses**	**Female workers**	**Male workers**	**Total workers**
Chemicals	C20: Manufacture of chemicals and chemical products	307,400	936,400	1,243,800
	C22: Manufacture of plastic and rubber products	374,600	1,242,400	1,617,000
Car manufacturing	C29: Manufacture of motor vehicles, trailers and semi-trailers -	665,400	2,639,500	3,304,900
Vehicle repair	G: Wholesale and Retail Trade; Repair of Motor Vehicles and Motorcycles	11,372,700	16,251,200	27,623,900

However, the Eurostat data for employment does not break down further than these broad categories and no other data has been identified regarding the specific breakdown of the sectors to a level that would enable identification of the numbers of potentially exposed workers with any given degree of accuracy. Any calculations will require the development of assumptions, but without information available to inform those assumptions, any resulting estimates will be subject to significant degrees of uncertainty.

A brief explanation of the difficulties in using the Eurostat data for the sectors using greases, lubricants and hydraulic fluids is presented below, along with a possible approach to providing at least some estimates, subject to the caveats made, is provided below.

Exposure to dodecyl phenols used to manufacture greases, lubricants and hydraulic fluids

Eurostat data only provide details of those employed at the level of G: Wholesale and retail trade; repair of motor vehicles and motorcycles (11,372,700 women workers aged 15-49 and 16,251,200 male workers aged 15+ in 2017) and C29: Manufacture of motor vehicles, trailers and semi-trailers (665,400 women workers aged 15-49 and 2,639,500 male workers aged 15+ in 2017). However, the

figures for G include many occupations on both the wholesale and retail side as well as on the repair side and do not enable estimates of those that actually use greases, lubricants and hydraulic fluids. Similarly, those for C29 similarly include many occupations which will have no contact with lubricants, greases (e.g. those involved in administration, sales and management, many vehicle construction line workers not requiring these substances in their work etc.).

A UK market report[600] published in 2018 indicated that employment in the motor vehicle maintenance and repair sector was 213,395 workers. A similar figure of 200,000 is suggested for the Motor Vehicle Repair sector by the UK Health and Safety Executive[601]. However, whilst these figures focus on the motor vehicle repair sector, they still include many occupations which will not involve contact with greases, lubricants and hydraulic fluids and would therefore not be appropriate to extrapolate to come up with overall estimates for the number of workers exposed.

It has therefore not been possible to discern from these or other sources any estimates of the number of workers actually using greases, lubricants or hydraulic fluids manufactured using any of the dodecyl phenol substances or even more generally.

In the absence of any data to inform the estimate of workers exposed to dodecyl phenols from using greases, lubricants and hydraulic fluids, a simple assumption of 1% of the total number of workers of reproductive age is to be assumed, with the resulting number being split 90% for male workers and 10% for female workers due to the fact that male employees are much more highly represented in the occupations likely to be involved in using greases etc. It is to be noted that the resulting estimates are highly uncertain, should be viewed with extreme caution and considered to be only for indicative purposes.

Applying this approach, the estimated number of workers potentially exposed to the 5 dodecyl substances used in greases, lubricants and hydraulic fluids are set out in Table X17-11 below.

Table X17-11: Indicative calculations for exposed workers working with greases, lubricants and hydraulic fluids

Sector	G: Wholesale and Retail Trade; Repair of Motor Vehicles and Motorcycles	C29: Manufacture of motor vehicles, trailers and semi-trailers
Total workers F	11,372,700	665,400
Total workers M	16,251,200	2,639,500
Total workers	27,623,900	3,304,900
Exposed workers (@1%)	276,239	33,049
Exposed workers F (10%)	27,624	3,305
Exposed workers M (90%)	248,615	29,744

Even if the above figures turn out to be somewhat accurate, it is important to note that they would only represent potential numbers of workers exposed to the substances and do not reflect numbers of workers exposed at levels above the threshold for effects.

Applying the same approach to the other sectors, the total numbers of exposed workers of reproductive age are set out in the following Table.

[600] https://www.ibisworld.co.uk/industry-trends/market-research-reports/wholesale-retail-trade/repair-of-motor-vehicles-motorcycles/motor-vehicle-maintenance-repair.html

[601] http://www.hse.gov.uk/mvr/resources/statistics/index.htm

Table X17-12: Numbers of exposed workers of reproductive age in sectors using dodecyl phenols				
Sector	**Total employed**	**Exposed**	**Exposed male**	**Exposed female**
G: Wholesale and Retail Trade; Repair of Motor Vehicles and Motorcycles	27,623,900	276239	248,615	27,624
C29: Manufacture of motor vehicles, trailers and semi-trailers	3,304,900	33,049	29,744	3,305
C20: Manufacture of chemicals and chemical products	1,243,800	12438	11,194	1,244
C22: Manufacture of plastic and rubber products	1,617,000	16170	14,553	1,617
Total	33,789,600	337,896	304,106	33,790

Estimates identified through literature review and consultation for this study

Neither of two industry associations responding to the consultation and that indicated that their members used dodecyl phenols had any data available on the number of workers that could be exposed, but one estimated that 90% of workers involved in production were male aged between 20 and 65.

When asked to estimate the duration, frequency, and level of exposure (e.g. air concentrations) for all or individual reprotoxic substances, one of the two associations indicated that "The requirements for working with reproductive toxicants are in Germany in the Hazardous Substances Ordinance and its subordinate regulations (inter alia TRGS 900) regulated. Accordingly, legally binding limit values are to be observed. Legal conformity is monitored by the local enforcement authorities." The other stated that "According to the members who responded in the internal consultation, the continuous exposure in extrusion processes during the work day is very low. In jointing and accessories production exposure is not frequent and occurs during testing, assembling and installation tasks. Exposure levels are extremely low." However it is noted that the associations' members cover a range of reprotoxic substances and it is not stated that the comments refer specifically to dodecyl phenols.

X17.5 Exposure levels

X17.5.1 Exposure routes

For dodecyl phenols in general, occupational exposure is generally quantified/regulated as inhalation exposure not oral exposure, although for some compounds dermal exposure may play a significant role, easily controlled through industrial hygiene control measures such as protective clothing and hand-wear.

X17.5.2 Current exposure levels

No information has been identified in literature or internet research on current levels of exposure to the dodecyl phenol substances. No EU or national level OELs have been identified either which could potentially have provided information on maximum exposure levels in different Member States

(assuming full compliance with these). As a result, available DNELs will be used to estimate current exposure levels to the different substances.

Table X17-13 below provides the established DNELs for the different substances and sets these against the thresholds established for the different health effects.

Table X17-13: DNELs and Thresholds for different health effects for Dodecyl phenols			
Substance	**Effect**	**Threshold (mg/m^3)**	**Systemic DNEL (mg/m^3)**
Phenol, dodecyl-, branched	Increased incidence of ovaries with decreased presence of corpora lutea (5 or less) (F1). Increased incidence of ovaries with decreased presence of corpora lutea (5 or less) (F0) Decreased epididymis sperm concentration(F0) Decreased vaginal patency (F1 females) Increased oestrous cycle length (F0) Increased oestrous cycle length (F1) Fertility index decreased Copulation index decreased Decrease in the ages of the first occurrence of oestrus Decreased number of implantation sites (F0) Decreased number of pups born (F2a) Decreased live litter size (F2a) Decreased pup body weight-male-PND 7 (F1) Decreased pup body weight-female-PND 7 (F1) Decreased pup body weight-female-PND 21 (F1) Increased incidence of skeletal malformations involving a curved scapula and/or abnormally shaped long bones	26.25 26.25 26.25 26.25 26.25 26.25 26.25 43.75 43.75 87.5 26.25 2.62 2.62 2.62 175	1.762
Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate)	As for Phenol, dodecyl-, branched		7.3[602]
Phenol, dodecyl-, sulfurized, carbonates, calcium salts	No registration dossier available, resulting in no threshold calculations		3.5
Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased	Pre-implantation loss	350	3.5
Phenol, dodecyl-,sulfurized, calcium salts	Increased number of dead pups at on lactation day 0 (F1 pups)	525	3.5
Phenol, dodecyl-,branched, sulfurized	As for Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased		3.526

X17.6 Current Risk Management Measures (RMMs)

X17.6.1 Overview of RMMs

Risk management measures are recommended for dodecyl compounds generally and include measures set out in Table X17-14 below.

[602] It is noted that the DNEL for Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate) is 7.3, higher than that for phenol, dodecyl, branched which is 1.762. Phenol, dodecyl-, branched is an impurity in Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate and therefore of much lower concentration in this substance.

Table X17-14: RMMs recommended for dodecyl phenols	
Area	**Measure**
Closed systems/engineering controls	Use in a closed-system
	Sufficient ventilation to remove and prevent build-up of vapours, dusts or fumes that could be generated during handling or thermal processing
Organisational measures	PPE to be determined by a qualified person
	Do not eat or drink; do not smoke when using the substance
	Wash hands before breaks and at the end of the work day
Respiratory protection	Wear respirator with dust filter; Air purifying respirator
Eye protection	Eye protection/ Chemical googles as per a health and safety professional (OSHA (29 CFR 1910.133) or EN166 (Europe)).
	Face shield for splash hazards; Safety glasses with side shields
Hand, Skin and body protection	Protective clothing and shoes/boots
	Wear gloves (rubber, nitrile, butyl) if dusty
	Impervious / protective gloves for prolonged contact (including instructions to wear other types than rubber gloves)

Recommendations provided in REACH registration dossiers that exist for five of the substances are provided in Table X17-15 below.

Table X17-15: Recommended RMMs for dodecyl substances from REACH registrations		
Substance	**Measure**	**Details**
Phenol, dodecyl-branched	Organisational measures	PPE to be determined by a qualified person
	Engineering measures	Sufficient ventilation to remove and prevent build-up of vapours, dusts or fumes that could be generated during handling or thermal processing
	Respiratory protection	Respirators as per a health and safety professional (OSHA (29 CFR 1910.133), ANSI (Z88.2-1992) or EN166 (Europe)); Maintain vapours, fumes or particulate levels below levels of concern (10 mg/m^3)
	Eye protection	Face shield for splash hazards; Safety glasses with side shields; Chemical googles if splashing is possible Eye protection as per a health and safety professional (OSHA (29 CFR 1910.133) or EN166 (Europe))
	Skin and body protection	Appropriate hand protection; impervious gloves for prolonged contact
Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased	Organisational measures	-
	Engineering measures	Use in a well ventilated area
	Respiratory protection	Not normally required; Where oil mist is generated and the occupational exposure limit for oil must is exceeded, then an approved respirator with adequate protection is required; For using air-purifying respirators, use a particulate cartridge
	Eye protection	Special eye protection is normally not required; Safety glasses with side shields is good practice if splashing is possible

Table X17-15: Recommended RMMs for dodecyl substances from REACH registrations		
Substance	**Measure**	**Details**
	Skin and body protection	Gloves (nitrile rubber, silver shield, or viton is recommended)
Phenol, dodecyl-, sulfurized, calcium salts	Organisational measures	-
	Engineering measures	Use in a well ventilated area
	Respiratory protection	Not normally required; Where oil mist is generated and the occupational exposure limit for oil must is exceeded, then an approved respirator with adequate protection is required; For using air-purifying respirators, use a particulate cartridge
	Eye protection	Special eye protection is normally not required; Safety glasses with side shields is good practice if splashing is possible
Phenol, dodecyl-, branched, sulfurized	Organisational measures	Handle in accordance with good industrial hygiene and safety practice
	Respiratory protection	For ordinary conditions of use- adequate ventilation Respirator with an approved filter in the case of vapour formation
	Eye protection	Tightly fitted safety goggles
	Skin and body protection	Use polyvinyl alcohol or butyl-rubber gloves; wash gloves with soap and water before removing; Use heat resistant gloves when handling hot material; Impervious clothing and choose according to the amount and concentration of the substance; Long sleeved clothing
	Other	Do not eat or drink; do not smoke when using the substance; wash hands before breaks and at the end of the work day
Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate)	Organisational measures	Use the substance in a well ventilated area. Appropriate PPE is required if the engineering controls or work practices are insufficient for preventing contact.
Sources: ECHA (2018): Phenol, dodecyl-, branched REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14705/9 ECHA (2018): Phenol, dodecyl-, sulfurized, calcium salts, overbased REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15042/9 ECHA (2018): Phenol, dodecyl-, sulfurized, calcium salts REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/13858/9 ECHA (2018): Phenol, dodecyl-, branched, sulfurized REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/13858/9 ECHA (2018); Zinc bis{bis(dodecylphenyl)] bis (dithiophosphate) REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/12713/9		

X17.7 Market analysis

Table X17-16 below provides data from Eurostat on the number of companies operating in 2016 in the broad sectors where dodecyl phenols are used. However, these are very broad sectors covering a significant number of sub-sectors and products, many of which do not involve the use of dodecyl

phenols. There were a total of 469,141 companies operating in the sub-sector NACE 45.20 Maintenance and repair of motor vehicles in 2015, but again, many of these companies will not use dodecyl phenols. Eurostat does also provide data for NACE 45.40 Sale, maintenance and repair of motorcycles and related parts and accessories, but this includes sales of motorcycles and parts/accessories as well as maintenance and repair, which is the specific sub-sector where greases, lubricants and hydraulic fluids containing dodecyl phenols are most likely to be used.

Similar issues apply to the other sectors where dodecyl phenols are used. For example, the sector C20: Manufacture of chemicals and chemical products includes all chemicals and intermediates and whilst literature and internet searches have identified that dodecyl phenols are mostly used in the manufacture of intermediates, it has not been possible to break this sown further to match with specific NACE codes.

Eurostat does not provide data at a lower level broken down by company size and it has not been possible to identify other sources of information, either through consultation or literature review, to obtain more appropriate estimates for the number of companies likely to be using dodecyl phenols.

Table X17-16: No. of enterprises in sectors where dodecyl phenols are used (2016)					
Sector	**Total**	**Micro**	**Small**	**Medium**	**Large**
G: Wholesale and retail trade; repair of motor vehicles and motorcycles	6,306,120	5,895,270	357,990	45,060	7,800
C29: Manufacture of motor vehicles, trailers and semi-trailers	19,700	12,200	3,900	2,280	1,320
C20: Manufacture of chemicals and chemical products	29,590	19,580	6,240	2,950	830
C22: Manufacture of rubber and plastic products	61,910	40,470	14,810	5,600	1,030

The socio-economic characteristics of the sectors in which BPA exposure may occur are summarised below.

- C20: Manufacture of chemicals and chemical products
- C22: Manufacture of rubber and plastic products
- C29: Manufacture of motor vehicles, trailers and semi-trailers
- G: Wholesale and retail trade; repair of motor vehicles and motorcycles.

X17.7.1 Number of SMEs in each sector

Table X17-17: Number and proportion of SMEs by size of enterprise and sector									
Sector	**TOTAL**	**Micro**		**Small**		**Medium**		**Large**	
	No. firms	**No. firms**	**% of total**	**No. firms**	**% of total**	**No. firms**	**% of total**	**No. firms**	**% of total**
C20	**29,590**	19,580	66%	6,240	21%	2,950	10%	830	3%
C22	**61,910**	40,470	65%	14,810	24%	5,600	9%	1,030	2%
C29	**19,700**	12,200	62%	3,900	20%	2,280	12%	1,320	7%
G	**6,306,120**	5,895,270	93%	357,990	6%	45,060	1%	7,800	0%
Source: Eurostat's Structural Business Statistics database									

X17.7.2 Average turnover by size of enterprise

Table X17-18: Average turnover by sector and size of enterprise, 2016												
Sector	Micro			Small			Medium			Large		
	Turnover /€m	No. firms	Ave. turnover / €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m
C20	13,281	19,580	0.68	34,247	6,240	5.49	132,655	2,950	44.97	346,366	830	417.31
C22	13,300	40,470	0.33	51,000	14,810	3.44	108,995	5,600	19.46	133,618	1,030	129.73
C29	5,688	12,200	0.47	14,643	3,900	3.75	59,377	2,280	26.04	952,917	1,320	721.91
G	-	5,895,270	-	-	357,990	-	-	45,060	-	-	7,800	-
Source: Eurostat's Structural Business Statistics database												

X17.7.3 R&D expenditure

Table X17-19: Business expenditure on R&D per sector (in € million), EU28		
Sector	Data availability	R&D expenditure (in €m)
C20	C20	6,659.7
C22	C22	2,371
C29	C29	28,456.9
G	G	4,387.9
Source: Eurostat Notes: EU28 totals do not include data for some member states, due to confidentiality.		

X17.8 Burden of ill health

X17.8.1 Cases of ill health

Table X17-20 provides a comparison between the DNELs for each of the dodecyl substances and the thresholds established for the different health effects identified for each substance. As can be seen, the thresholds are higher than the DNELs in all cases, implying that there would be no cases of the different health effects under a scenario where all uses were compliant with the DNELs.

Considering a more conservative scenario where exposure is actually higher than the established DNELs (e.g. in cases of non-compliance) and taking a value of 10x DNEL suggests that there are only 3 potential health effects of relevance from the exposure of workers to all of the dodecyl phenol substances, and these relate to phenol dodecyl, branched.

Table X17-20: Comparison of thresholds with DNELs for different health effects			
Health effect	DNEL (mg/m^3)	10x DNEL (mg/m3)	Threshold (mg/m^3)
Phenol, dodecyl-, sulfurized, calcium salts (CAS 68855-45-8)			
Increased number of dead pups at on lactation day 0 (F1 pups)	3.5	35	525

Table X17-20: Comparison of thresholds with DNELs for different health effects			
Health effect	**DNEL (mg/m^3)**	**10x DNEL (mg/m3)**	**Threshold (mg/m^3)**
Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased (CAS 68784-26-9)[603]			
Pre-implantation loss	3.5	35	350
Phenol, dodecyl-, branched (CAS 121158-58-5)[604]			
Increased incidence of ovaries with decreased presence of corpora lutea (5 or less) (F1)	1.762	17.62	26.25
Increased incidence of ovaries with decreased presence of corpora lutea (5 or less) (F0)	1.762	17.62	26.25
Decreased epididymis sperm concentration(F0)	1.762	17.62	26.25
Decreased vaginal patency (F1 females)	1.762	17.62	26.25
Increased oestrous cycle length (F0)	1.762	17.62	26.25
Increased oestrous cycle length (F1)	1.762	17.62	26.25
Fertility index decreased	1.762	17.62	43.75
Copulation index decreased	1.762	17.62	43.75
Decrease in the ages of the first occurrence of oestrus	1.762	17.62	87.5
Decreased number of implantation sites (F0)	1.762	17.62	26.25
Decreased number of pups born (F2a)	1.762	17.62	26.25
Decreased live litter size (F2a)	1.762	17.62	26.25
Decreased pup body weight-male-PND 7 (F1)	1.762	17.62	2.62
Decreased pup body weight-female-PND 7 (F1)	1.762	17.62	2.62
Decreased pup body weight-female-PND 21 (F1)	1.762	17.62	2.62
Increased incidence of skeletal malformations involving a curved scapula and/or abnormally shaped long bones	1.762	17.62	175

However, these effects highlighted in the above table are at 7 and 21 days after birth and it impossible to say whether the effects are due to a reproduction effect or a failure to thrive after birth. It is noted in the CLH report[605] from 2010 that the study on which these health effects were observed was a multi-generational study, treating both male and female rats, but that as a result of being exposed to the substance, the mothers were identified as suffering from reduced weight and consequently were not thriving themselves. This being the case, it is impossible to conclude with any certainty that the low body weight of their offspring was a result of a reprotoxic effect rather than due to the poor health of the mother.

Consequently, no cases of ill health have been definitively identified as a result of exposure to any of the dodecyl phenol substances.

[603] Data from Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased (CAS 68784-26-9) can be read across to Phenol, dodecyl-, branched, sulfurized. There is no registration dossier for Phenol, dodecyl-, sulfurized, carbonates, calcium salts, so not possible to estimate the number of cases.

[604] Data from Phenol, dodecyl-, branched can be read across to Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate). Whilst the DNEL for Zinc bis[bis(dodecylphenyl)] bis(dithiophosphate) is higher than that for Phenol, dodecyl-, branched, it has been assumed to be the same in these calculations due to the fact that Phenol, dodecyl-, branched is an impurity in the substance.

[605] CLH report - Proposal for Harmonised Classification and Labelling based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2 Substance Name: Phenol, dodecyl-, branched

Annex 18 Organotins

X18.1 Introduction

X18.1.1 Relevant substance(s)

Organostannic or organotin compounds (organotins) are substances composed of tin directly bound to a number of organic groups. According to the number of organic groups, organotins can be classified in four distinct classes: monoorganotins (RSnX3), diorganotins (R2SnX2), triorganotins (R3SnX) and tetraorganotins (R4Sn).[606]

They are characterised by the presence of a strong carbon-tin bond and have the general formula: RXSnL(4-X), where R denotes an organic alkyl or aryl group and L denotes one or more organic (or sometimes inorganic) ligands which may or may not be the same. In general, the properties of organotin compounds vary significantly depending upon their structure.[607] The chemical and physical properties of organotin compounds vary, depending mainly upon the number and nature of the R groups, but also upon the type of ligand (X). Organotins solubility in water, for instance, tends to decrease with both the increase in the number and length of the organic substituents; however, the nature of the ligand can also play an important role).[608] Moreover, the toxicity of organotins also varies greatly, being strongly influenced by the number and nature of the organic groups. In general, inorganic tin is non-toxic, whereas trisubstituted compounds have maximum toxicological activity.[608] [609]

Organotins exhibit both lipophilic and ionic properties; therefore, they can accumulate in lipids and they can also bind to proteins such as glutathione and a-keratins.[610] Due to this dual behaviour, organotins detection is expected in such distinct matrices such as liver, kidney, blood, hair and nails, urine or breast milk.[606]

Organotins have numerous commercial uses, particularly in polymers and coatings. Tributyltins had been widely used as antifoulant coatings but their high toxicity to marine organisms and contamination of food and the environment resulted in an international ban. Dialkyltins (including those described in this report) are used as catalysts for polyurethanes and stabilizers for polyvinyl chloride, and as a result, in addition to industrial applications, can find their way into consumer applications such as automotive and building materials, piping for drinking water, adhesives, sealants, as well as food packaging & contact.

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[606] Sousa et al, 2014, "History on organotin compounds, from snails to humans", article in *Environmental Chemistry Letters*, March 2014, available at: http://agris.fao.org/agris-search/search.do?recordID=US201400147662

[607] RAR, 2005, "Risk Assessment Studies on Targeted Consumer Applications of Certain Organotin Compounds", prepared for DG Enterprise and Industry by Risk & Policy Analysts Ltd (RPA), available at: https://ec.europa.eu/docsroom/documents/13041/attachments/1/translations/en/renditions/native

[608] Hoch, M, 2001, "Organotin compounds in the environment: an overview", *Appl Geochem*m 16(7–8):719–743, available at: https://www.sciencedirect.com/science/article/pii/S0883292700000676?via%3Dihub

[609] Sekizawa J, Sutur G, Birnbaum Lm, 2003, "Integrated human and ecological risk assessment: a case study of tributyltin and triphenyltin compounds", *Hum Ecol Risk Assess*, 9(1):325–342, available at: https://www.tandfonline.com/doi/abs/10.1080/718990536

[610] Appel KE, 2004, "Organotin compounds: toxicokinetic aspects", *Drug, Metab Rev* 36(3–4):763–786, available at: https://www.tandfonline.com/doi/full/10.1081/DMR-200033490

The substances that have been selected for this study are[611]:

- Dibutyltin dilaurate (EC No: 201-861-7; CAS No: 77-58-7);
- Dibutyltin dichloride (EC No: 211-670-7; CAS No: 683-18-1);
- 2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate (EC No: 239-622-4; CAS no: 15571-58-1);
- Dibutyltin oxide (EC No: 212-449-1; CAS No: 818-08-6); and
- Dibutyltin bis (2-ethylhexanoate) (EC No: 220-481-2; CAS No: 2781-10-4).

Each organotin compoud is known under a wide range of other chemical/trade names. A full list of alternative names can be found in the table below:

Table X18-1: Alternative names for organotin compounds

Compound/Type of name	Regulatory process names	Trade names
Dibutyltin dilaurate	Dibutyltin dilaurate; dibutyltin dilaurate; dibutyl[bis(dodecanoyloxy)]stannane	BRB DBTDL; D-22; DBTDL; Dibutyltindilaurate (DBT); Fomrez SUL-4E; Fomrez« catalyst SUL-4; Mark DBTL; Metatin(TM) Catalyst 712E; Metatin(TM) Catalyst 712ES; Metatin(TM) Katalysator 712E; Metatin(TM) Katalysator 712ES; SILOPREN CATALYST 162; Songstab TL-100; Songstab TL-191; Tinstab BL277
Dibutyltin dichloride	DBTC; Dibutyltin dichloride; Dibutyltin dichloride (DBTC); dibutyltin dichloride	Axion CS 2430; DBTCl; DIBUTYLDICHLOROSTANNANE; dibutyltindichloride; (DBTC); Tin dibutyl-dichloride
2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate	2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate; 2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate (DOTE); 2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate; 8-Oxa-3,5-dithia-4-stannatetradecanoic acid, 10-ethyl-4,4-dioctyl-7-oxo-, 2-ethylhexyl ester	10-éthyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatétradecanoate de 2-éthylhexyle; 2-Ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate; 8-Oxa-3,5-dithia-4-stannatetradecanoic acid, 10-ethyl-4,4-dioctyl-7-oxo-, 2-ethylhexyl ester; Thermolite 890
Dibutyltin oxide	Dibutyltin oxide; dibutyltin oxide	Axion CS 2455; Axion CS 2455W; Axion CS 2460; DBTO; Mark DBTO; SONGCAT DBTO
Dibutyltin bis (2-ethylhexanoate)	Dibutyltin bis(2-ethylhexanoate); dibutyltin bis(2-ethylhexanoate)	T634; T634_K1; T634_Komp1
Sources: ECHA (2018)[611]		

Chemical formulas and chemical structures of the five chosen organotin compouds are shown in Figure X18-1 overleaf:

[611] ECHA, 2018, "Registered Substances database", available at: https://echa.europa.eu/information-on-chemicals/registered-substances [accessed 31/07/2018]

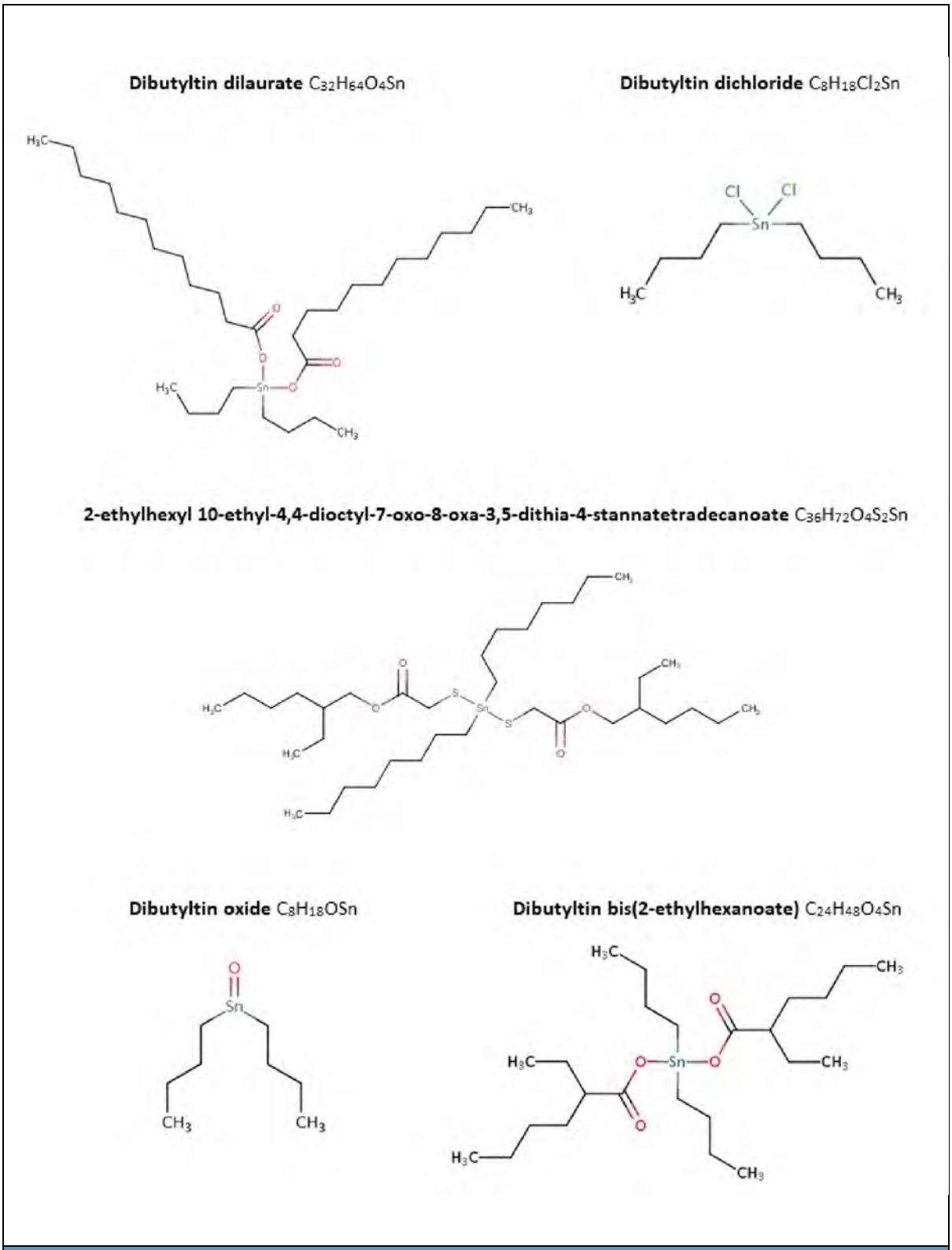

Figure X18-1: Organotin compounds– chemical structures
Source*: *ECHA[612]; EPA[613]

X18.1.2 Hazard classification(s)

The following classifications have been identified for the 5 selected organotin compounds:

Dibutyltin dilaurate[614]

- Reproductive toxicity (**Repr. 1B**) - (Hazard Statement Code H360FD: May damage fertility. May damage the unborn child);
- Germ cell mutagenicity (**Muta. 2**)- (Hazard Statement Code H314: Suspected of causing genetic defects; and
- Specific target organ toxicity- repeated exposure (**STOT RE-1**) – (Hazard Statement Code H372: Causes damage to organs (immune system) through prolonged or repeated exposure)

Dibutyltin dichloride[615]

- Reproductive toxicity (**Repr. 1B**) - (Hazard Statement Code H360FD: May damage fertility. May damage the unborn child);
- Skin corrosion (Skin Corr. 1B)- (Hazard Statement Code H314: Causes severe skin burns and eye damage);
- Germ cell mutagenicity (**Muta. 2**)- (Hazard Statement Code H314: Suspected of causing genetic defects;
- Specific target organ toxicity (**STOT RE-1**) – (Hazard Statement Code H372: Causes damage to organs through prolonged or repeated exposure);
- Acute toxicity (**Acute Tox. 3**) – (Hazard Statement Code H301: Toxic if swallowed);
- Acute toxicity (**Acute Tox. 4**) – (Hazard Statement Code H312: Harmful in contact with skin);
- Acute toxicity (**Acute Tox. 2**) – (Hazard Statement Code H330: Fatal if inhaled);
- Acute aquatic toxicity (**Aquatic Acute 1**) – (Hazard Statement Code H400: Very toxic to aquatic life); and
- Chronic aquatic toxicity (**Aquatic Chronic 1**) – (Hazard Statement Code H410: Very toxic to aquatic life with long lasting effects)

2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate[616]

- Reproductive toxicity (**Repr. 1B**) – (Hazard Statement Code H360D: May damage the unborn child)

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[612] ECHA, 2018, "Substance Information - 2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate, available at: https://echa.europa.eu/substance-information/-/substanceinfo/100.036.005

[613] EPA, 2018, Substance information for bis(2-ethylhexanoate: https://comptox.epa.gov/dashboard/dsstoxdb/results?search=Dibutyltin%20bis(2-ethylhexanoate) ; Dibutyltin oxide: https://comptox.epa.gov/dashboard/dsstoxdb/results?search=Dibutyltin%20oxide ; 2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate: https://comptox.epa.gov/dashboard/dsstoxdb/results?search=dota ; Dibutyltin dichloride: https://comptox.epa.gov/dashboard/dsstoxdb/results?search=Dibutyltin%20dichloride ; Dibutyltin dilaurate: https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID6024961

[614] ECHA, 2018, "Summary of Classification and Labelling - Dibutyltin dilaurate", available at: https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/58627 [accessed 31/07/2018]

[615] ECHA, 2018, "Summary of Classification and Labelling - Dibutyltin dichloride", available at: https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/14220 [accessed 31/07/2018]

[616] ECHA, 2018, "Summary of Classification and Labelling - 2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate", available at: https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/12637 [accessed 31/07/2018]

Dibutyltin oxide[617]

- Reproductive toxicity (**Repr. 1B**) – (Hazard Statement Code H360: May damage fertility or the unborn child);
- Skin irritation (**Skin Irrit. 2**) – (Hazard Statement Code H315: Causes skin irritation);
- Acute toxicity (**Acute Tox. 3**) – (Hazard Statement Code H301: Toxic if swallowed);
- Serious eye damage (**Eye Dam. 1**) – (Hazard Statement Code H318: Causes serious eye damage);
- Skin sensitisation (**Skin Sens. 1**) – (Hazard Statement Code H317: May cause an allergic skin reaction);
- Germ cell mutagenicity (**Muta. 2**) – (Hazard Statement Code H341: Suspected of causing genetic defects);
- Specific target organ toxicity – single exposure (**STOT SE 1**) – (Hazard Statement Code H370: Causes damage to organs (thymus);
- Specific target organ toxicity – repeated exposure (**STOT RE 1)** - (Hazard Statement Code H372: Causes damage to organs (thymus); and
- Chronic aquatic toxicity (**Aquatic Chronic 1**) – (Hazard Statement Code H410: Very toxic to aquatic life with long lasting effects)

Dibutyltin bis (2-ethylhexanoate)[618]

- Reproductive toxicity (**Repr. 1B**) – (Hazard Statement Code H360: May damage fertility or the unborn child);
- Skin sensitisation (**Skin Sens. 1**) – (Hazard Statement Code H317: May cause an allergic skin reaction);
- Skin corrosion (**Skin Corr. 1B**) – (Hazard Statement Code H314: Causes severe skin burns and eye damage);
- Acute aquatic toxicity (**Aquatic Acute 1**) – (Hazard Statement Code H400: Very toxic to aquatic life): and
- Chronic aquatic toxicity (**Aquatic Chronic 1**) – (Hazard Statement Code H410: Very toxic to aquatic life with long lasting effects).

X18.1.3 Existing OELs and BLVs

The OELs in EU Member States and key non-EU countries are summarised below. In addition, Czech Republic has designated organotin compounds as dermal irritants. There are no *Biological Limit Values (BLVs)* set for organotin compounds in the EU.

Table X18-2: OELs for organotin compounds (as Sn) in the EU and key non-EU countries					
Country	OELs 8-hr TWA, in mg/m^3 Binding (unless stated otherwise)				
	Dibutyltin dilaurate	Dibutyltin dichloride	2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate	Dibutyltin oxide	Dibutyltin bis (2-ethylhexanoate)
EU member states					

[617] ECHA, 2018, "Summary of Classification and Labelling - Dibutyltin oxide", available at: https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/62167 [accessed 31/07/2018]

[618] ECHA, 2018, "Summary of Classification and Labelling - Dibutyltin bis (2-ethylhexanoate)", available at: https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/72698 [accessed 31/07/2018]

Table X18-2: OELs for organotin compounds (as Sn) in the EU and key non-EU countries					
Country	OELs 8-hr TWA, in mg/m³ Binding (unless stated otherwise)				
	Dibutyltin dilaurate	Dibutyltin dichloride	2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate	Dibutyltin oxide	Dibutyltin bis (2-ethylhexanoate)
Austria	0.1	0.1	n/a	0.1	n/a
Belgium	0.1	0.1	n/a	0.1	n/a
Bulgaria	0.1	0.1	n/a	0.1	n/a
Croatia	0.1	0.1	n/a	0.1	n/a
Cyprus	n/a	n/a	n/a	n/a	n/a
Czech Republic	0.1	0.1	n/a	0.1	n/a
Denmark	n/a	n/a	n/a	n/a	n/a
Estonia	0.1	0.1	n/a	0.1	n/a
Finland	0.1	0.1	n/a	0.1	n/a
France	0.1	0.1	n/a	0.1	n/a
Germany	0.1	0.009 (Inhalable fraction and vapour)	0.01 (Inhalable fraction and vapour)	n/a	n/a
Greece	0.1	0.1	n/a	0.1	n/a
Hungary	0.1	0.1	n/a	0.1	n/a
Ireland	0.1	0.1	n/a	0.1	n/a
Italy	0.1	0.1	n/a	0.1	n/a
Latvia	n/a	n/a	n/a	n/a	n/a
Lithuania	0.1	0.1	n/a	0.1	n/a
Luxembourg	n/a	n/a	n/a	n/a	n/a
Malta	n/a	n/a	n/a	n/a	n/a
Netherlands	n/a	n/a	n/a	n/a	n/a
Poland	n/a	n/a	n/a	n/a	n/a
Portugal	0.1	0.1	n/a	0.1	n/a
Romania	0.05	0.05	n/a	0.05	n/a
Slovakia	0.1	0.1	n/a	0.1	n/a
Slovenia	0.1	0.1	n/a	0.1	n/a
Spain	0.1	0.1	0.1	0.1	0.1
Sweden	0.1	0.1	n/a	0.1	n/a
United Kingdom	0.1	0.1	n/a	0.1	n/a
Non-EU countries					
Japan	n/a	n/a	n/a	n/a	n/a
US	0.1	0.1	n/a	0.1	n/a
Canada	0.1	0.1	n/a	0.1	n/a
China	0.1	n/a	n/a	n/a	n/a
India	n/a	n/a	n/a	n/a	n/a
Korea	n/a	n/a	n/a	n/a	n/a
Brazil	n/a	n/a	n/a	n/a	n/a
Australia	n/a	n/a	n/a	n/a	n/a
Sources: DGUV Gestis, http://limitvalue.ifa.dguv.de/					

The DNELs (Derived No Effect Levels)[619] for occupational exposure to each of the five selected organotin compounds are summarised in table below.

Table X18-3: DNELs for organotin compounds in the EU			
Population	**Exposure Route**	**DNEL (mg/m³* or mg/kg bw/day)**	**Most sensitive endpoint**
Dibutyltin dilaurate			
Workers	Inhalation (Long term)	0.02*	Inhalation (Long term)
	Dermal (Long term)	0.43	Dermal (Long term)
	Dermal (Short term)	2.08	Dermal (Short term)
Dibutyltin dichloride			
Workers	Inhalation (Long term)	0.01*	Repeated dose toxicity
	Inhalation (Short term)	0.07*	developmental toxicity/teratogenicity
	Dermal (Long term)	0.2	Repeated dose toxicity
	Dermal (Short term)	1	developmental toxicity/teratogenicity
2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate			
Workers	Inhalation (Long term)	0.062*	Repeated dose toxicity
Dibutyltin oxide			
Workers	Inhalation (Long term)	0.01*	Repeated dose toxicity
	Inhalation (Short term)	0.07*	developmental toxicity/teratogenicity
	Dermal (Long term)	0.2	Repeated dose toxicity
	Dermal (Short term)	1	developmental toxicity/teratogenicity
Dibutyltin bis (2-ethylhexanoate)			
Workers	Inhalation (Long term)	0.01*	Repeated dose toxicity
	Inhalation (Short term)	0.07*	developmental toxicity/teratogenicity
	Dermal (Long term)	0.2	Repeated dose toxicity
	Dermal (Short term)	1	developmental toxicity/teratogenicity
Source: ECHA REACH registration dossiers Notes: DNEL values marked with a "*" are in mg/m³.			

[619] ECHA REACH registration dossiers:
Dibutyltin dilaurate, https://echa.europa.eu/registration-dossier/-/registered-dossier/14904
Dibutyltin dichloride, https://echa.europa.eu/information-on-chemicals/registered-substances/-/disreg/substance/100.010.610
2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate, https://echa.europa.eu/registration-dossier/-/registered-dossier/14171/7/1
Dibutyltin oxide, https://echa.europa.eu/registration-dossier/-/registered-dossier/14790
Dibutyltin bis(2-ethylhexanoate), https://echa.europa.eu/registration-dossier/-/registered-dossier/11664/7/1

Table X18-4: DNELs for organotin compounds in the EU			
Population	**Exposure Route**	**DNEL (mg/m³* or mg/kg bw/day)**	**Most sensitive endpoint**
Dibutyltin dilaurate			
Workers	Inhalation (Long term)	0.02*	Inhalation (Long term)
	Dermal (Long term)	0.43	Dermal (Long term)
	Dermal (Short term)	2.08	Dermal (Short term)
General population	Inhalation (Long term)	0.005*	Repeated dose toxicity
	Inhalation (Short term)	0.04*	developmental toxicity/teratogenicity
	Dermal (Long term)	0.16	Repeated dose toxicity
	Dermal (Short term)	0.5	immunotoxicity
	Oral (Long term)	0.003	Repeated dose toxicity
	Oral (Short term)	0.02	developmental toxicity/teratogenicity
Dibutyltin dichloride			
Workers	Inhalation (Long term)	0.01*	Repeated dose toxicity
	Inhalation (Short term)	0.07*	developmental toxicity/teratogenicity
	Dermal (Long term)	0.2	Repeated dose toxicity
	Dermal (Short term)	1	developmental toxicity/teratogenicity
General population	Inhalation (Long term)	0.003*	Repeated dose toxicity
	Inhalation (Short term)	0.02#	developmental toxicity/teratogenicity
	Dermal (Long term)	0.08	Repeated dose toxicity
	Dermal (Short term)	0.5	developmental toxicity/teratogenicity
	Oral (Long term)	0.002	Repeated dose toxicity
	Oral (Short term)	0.01	developmental toxicity/teratogenicity
2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate			
Workers	Inhalation (Long term)	0.062#	Repeated dose toxicity
General population	Oral (Long term)	0.001	Repeated dose toxicity
Dibutyltin oxide			
Workers	Inhalation (Long term)	0.01#	Repeated dose toxicity
	Inhalation (Short term)	0.07#	developmental toxicity/teratogenicity
	Dermal (Long term)	0.2	Repeated dose toxicity
	Dermal (Short term)	1	developmental toxicity/teratogenicity
General population	Inhalation (Long term)	0.003#	Repeated dose toxicity
	Inhalation (Short term)	0.02#	developmental toxicity/teratogenicity
	Dermal (Long term)	0.08	Repeated dose toxicity
	Dermal (Short term)	0.5	developmental toxicity/teratogenicity

Table X18-4: DNELs for organotin compounds in the EU			
Population	**Exposure Route**	**DNEL (mg/m³* or mg/kg bw/day)**	**Most sensitive endpoint**
	Oral (Long term)	0.002	Repeated dose toxicity
	Oral (Short term)	0.01	developmental toxicity/teratogenicity
Dibutyltin bis (2-ethylhexanoate)			
Workers	Inhalation (Long term)	0.01#	Repeated dose toxicity
	Inhalation (Short term)	0.07#	developmental toxicity/teratogenicity
	Dermal (Long term)	0.2	Repeated dose toxicity
	Dermal (Short term)	1	developmental toxicity/teratogenicity
General population	Inhalation (Long term)	0.003#	Repeated dose toxicity
	Inhalation (Short term)	0.02#	developmental toxicity/teratogenicity
	Dermal (Long term)	0.08	Repeated dose toxicity
	Dermal (Short term)	0.5	developmental toxicity/teratogenicity
	Oral (Long term)	0.002	Repeated dose toxicity
	Oral (Short term)	0.01	developmental toxicity/teratogenicity
Source: ECHA REACH registration dossiers			

X18.1.4 Legislation other than CAD

This section screens out the uses that are mentioned in literature but that are no longer relevant due to regulatory or voluntary phase outs.

REACH restrictions

Several uses of Organostannic compounds are restricted under REACH. [620]

In accordance with entry No. 20 of Annex XVII to Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), (OJ L 396, 30.12.2006, p. 1-849), pursuant to Commission Regulation (EC) No 552/2009 of 22 June 2009 amending Regulation (EC) No 1907/2006 (REACH) as regards Annex XVII (OJ L 164, 26.6.2009, p. 7-31), and Commission Regulation(EU) No 276/2010 of 31 March 2010 amending Regulation (EC) No 1907/2006 (REACH) as regards Annex XVII (OJ L 86, 1.4.2010, p. 7-12), the following applies to all Organostannic compounds:

1. Shall not be placed on the market, or used, as substances or in mixtures where the substance or mixture is acting as biocide in free association paint;

[620] Commission Regulation (EC) No 552/2009 of 22 June 2009 amending Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards Annex XVII (Text with EEA relevance), available at: https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX:32009R0552

2. Shall not be placed on the market, or used, as substances or in mixtures where the substance or mixture acts as biocide to prevent the fouling by micro-organisms, plants or animals of:

    (a) all craft irrespective of their length intended for use in marine, coastal, estuarine and inland waterways and lakes;

    (b) cages, floats, nets and any other appliances or equipment used for fish or shellfish farming;

    (c) any totally or partly submerged appliance or equipment.

3. Shall not be placed on the market, or used, as substances or in mixtures where the substance or mixture is intended for use in the treatment of industrial waters.

The following applies to Dibutyltin (DBT) compounds[620]:

a) Dibutyltin (DBT) compounds shall not be used after 1 January 2012 in mixtures and articles for supply to the general public where the concentration in the mixture or the article, or part thereof, is greater than the equivalent of 0.1 % by weight of tin.

b) Articles and mixtures not complying with point (a) shall not be placed on the market after 1 January 2012, except for articles that were already in use in the Community before that date.

c) By way of derogation, points (a) and (b) shall not apply until 1 January 2015 to the following articles and mixtures for supply to the general public:

- one-component and two-component room temperature vulcanisation sealants (RTV-1 and RTV-2 sealants) and adhesives;
- paints and coatings containing DBT compounds as catalysts when applied on articles,
- soft polyvinyl chloride (PVC) profiles whether by themselves or coextruded with hard PVC;
- fabrics coated with PVC containing DBT compounds as stabilisers when intended for outdoor applications; and
- outdoor rainwater pipes, gutters and fittings, as well as covering material for roofing and façades.

d) By way of derogation, points (a) and (b) shall not apply to materials and articles regulated under Regulation (EC) No 1935/2004.

Furthermore, the following applies to dioctyltin compounds[620]:

a) Dioctyltin (DOT) compounds shall not be used after 1 January 2012 in articles for supply to the general public where the concentration in the article, or part thereof, is greater than the equivalent of 0.1 % by weight of tin:

- textile articles intended to come into contact with the skin;
- gloves;
- footwear or part of footwear intended to come into contact with the skin;
- wall and floor coverings;
- childcare articles;
- female hygiene products;

- nappies; and
- two-component room temperature vulcanisation moulding kits (RTV-2 moulding kits).

The PIC regulation

The Prior Informed Consent Regulation administers the import and export of certain hazardous chemicals and places obligations on companies who wish to export these chemicals to non-EU countries. The PIC Regulation applies to a list of entries (for individual chemicals or groups of chemicals), which are included in Annex I, and to mixtures containing such chemicals in a concentration that triggers labelling obligations under the CLP Regulation (EC) No 1272/2008 (irrespective of the presence of any other substance), as well as to articles containing these chemicals in an unreacted form.

This list is updated regularly as a result of regulatory actions under EU legislation, and developments under the Rotterdam Convention. It is divided into three parts that define the different obligations applied to the chemicals.[621]

All five Organostannic compounds are listed in Annex I Part 1 under industrial chemicals for public use, and are subject to export notification procedure.

X18.2 Summary of health endpoints, thresholds & DRRs

X18.2.1 Relevant health endpoints

Relevant reproductive health endpoints

Literature review has been undertaken to determine the relevant reproductive health endpoints for exposure to organotin compounds. Those effects identified that have been deemed to be potentially relevant to humans are listed in tables below.

The health effects have also been grouped into the following groups along with their threshold doses:

- Fertilisation/implantation; and
- Embroynic/foetal development.

For 2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate (EC No: 239-622-4; CAS no: 15571-58-1), no effect on reproductive organs or reproductive capacity was observed up to and including the highest dose tested.[622]

There is a lack of relevant information on reproductive and developmental effects as a result of exposure to and Dibutyltin bis (2-ethylhexanoate) (EC No: 220-481-2; CAS No: 2781-10-4). To address this issue, the following organotin compounds have been identified as suitable proxies:

- Dibutyltin diacetate (DBTA; EC Number: 213-928-8; CAS Number: 1067-33-0);
- Dibutyltin maleate (DBTM; EC Number 201-077-5; CAS Number 78-04-6); and
- Butyl(3-hydroxybutyl)tin dilaurate (3-OHDBTL; CAS Number 153759-62-7).

[621] PIC regulation on ECHA, "List of chemicals Annex I", available at: https://echa.europa.eu/regulations/prior-informed-consent/list-chemicals

[622] REACH registration dossier for 2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate, available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14171

The information and data available for these three compounds will be used to derive DRRs, which may be used to describe effects of exposure to Dibutyltin bis (2-ethylhexanoate). 3-OHDTBL is a metabolite of dibutyltins and can act as a more sensitive proxy.

Table X18-5: Relevant reproductive health endpoints for Dibutyltin dilaurate				
Group	**Effects seen**	**Threshold dose (mg/kg/ day) (no effects)**	**Converted Threshold dose (mg/ m³) (no effects)**	**Effects in humans**
Embryonic/ foetal development	Increased mandible complications[623]	5.05	8.84	Expected
	Anomaly of mandibular fixation, cranial hypoplasia, and fused ribs[623]	5.05	8.84	Expected

Table X18-6: Relevant reproductive health endpoints for Dibutyltin dichloride				
Group	**Effects seen**	**Threshold dose (mg/kg/ day) (no effects)**	**Converted Threshold dose (mg/ m³) (no effects)**	**Effects in humans**
zFertilisation/ implantation	Higher number of non-pregnant females[624]	3.80	6.65	Expected
	Higher pre-implantation loss	3.80	6.65	Expected
	Increased number of litters totally resorbed[Error! Bookmark not defined.]	7.60	13.3	Expected
	Increased number of resorptions and dead foetuses per litter in early stage[Error! Bookmark not defined.]	3.80	6.65	Expected
	Increased post-implantation loss per litter[625]	0.38	0.67	Expected
	Higher incidence of post-implantation loss per litter[625]	5.00	8.75	Expected
	Higher incidence of post-implantation loss per litter[625]	1.00	1.75	Expected
	Increased post-implantation loss[626] [627]	1.5	2.63	Expected
	Decreased number of live foetuses per litter[624]	3.80	6.65	Expected
	Increased Pup mortality (F1) [626]	1.5	2.63	Expected

[623] Noda T, Morita S, Baba A., 1993, Toxicology, 85:2–3, 149-160, as cited in ECHA registration dossier for dibutyltin dilaurate

[624] Ema M, & Harazono, A. (2000) Reprod. Toxicol. 14, 451–456, as described in CLH Report for Dibutyltin Dilaurate, Norwegian Environment Agency, version 2.0, 2014

[625] Ema et al 1995, JOURNAL OF APPLIED TOXICOLOGY, VOL. 15(4), 297-302 (1995) as cited in the dossier for Dibutyltin dichloride CAS 683-18-1

[626] ECHA Registration Dossier for Dibutyltin dichloride; 2003 Unnamed Study Report.

[627] **Doses of 0, 5, 30 and 200 mg/kg diet are equivalent to 0, 0.25, 1.5 and 10 mg/kg bw/day by WHO formula 'Mean factors for converting concentrations of substances in feed into a daily dose for rats in subacute, study' (Multiplied with a factor 0.05 here) http://www.efsa.europa.eu/sites/default/files/consultation/110707a.pdf

Table X18-6: Relevant reproductive health endpoints for Dibutyltin dichloride				
Group	**Effects seen**	**Threshold dose (mg/kg/ day) (no effects)**	**Converted Threshold dose (mg/ m^3) (no effects)**	**Effects in humans**
	Higher number of resorptions and dead foetuses per litter[628]	5.00	8.75	Expected
	Increased incidence of totally resorbed litters[629]	20	35	Expected
	Increased incidence of litters totally resorbed[625]	10.0	17.5	Expected
	Decreased survival rate of foetuses at terminal caesarean sectioning[630]	0.25	0.88	Expected
	Decreased number of females with live-born pups[626]	1.5	2.63	Expected
	Decreased number of pups delivered[626]	1.5	2.63	Expected
	Decreased number of live-born pups[626]	1.5	2.63	Expected
	Lower number of live foetuses per litter[628]	5.00	8.75	Expected
	Lower number of live foetuses per litter[625]	1.00	1.75	Expected
	Decreased placental weight [628]	2.50	4.38	Expected
	Pup weight decreased on PN 4 (F1) [626]	1.5	2.63	Expected
	Decreased Gestation index[626]	1.5	2.63	Expected
	Pup weight decreased on PN 1 (F1) [626]	1.5	2.63	Expected
Embryonic/ foetal development	Increased incidence of ovarian cysts in high-dose females[626]	1.5	2.63	Expected
	Decreased body weights of live fetuses[628]	2.50	4.38	Expected
	High incidence of foetuses with malformations (Cleft jaw and ankyloglossia were the most frequent malformations observed in the affected foetuses) [628]	2.50	4.38	Expected
	Increase in the incidence of foetuses with skeletal malformations[628]	2.50	4.38	Expected
	Increased incidence of foetuses with skeletal anomalies[629]	2	3.5	Expected
	Increase in the incidence of foetuses with skeletal malformations[629]	2	3.5	Expected
	Increased incidence of fused ribs and deformed vertebral column[628]	2.50	4.38	Expected
	Increase in the incidence of foetuses with external malformations[629]	2	3.5	Expected

[628] Ema et al 1991, Toxicology Letters, 58 (1991) 347-356 as cited in the dossier for Dibutyltin dichloride CAS 683-18-1

[629] Ema et al 1992, Toxicology, 73 (1992) 81-92 as cited in the dossier for Dibutyltin dichloride CAS 683-18-1

[630] Ema M, Fukunishi K, Matsumoto M, Hirose A, Kamata E, Ihara T (2007). Developmental toxicity of dibutyltin dichloride in cynomolgus monkeys. Reprod Toxicol. 23(1), 12-9

Table X18-6: Relevant reproductive health endpoints for Dibutyltin dichloride				
Group	**Effects seen**	**Threshold dose (mg/kg/ day) (no effects)**	**Converted Threshold dose (mg/ m^3) (no effects)**	**Effects in humans**
	Increase in the incidence of foetuses with external malformation[629]	1.00	1.75	Expected
	Higher incidence of foetuses with internal malformations[628]	2	3.5	Expected
	Increased incidence of foetuses with internal malformations[625]	1.00	1.75	Expected
	Increased mandible complications[631]	2.43	4.25	Expected
	Increased incidences of foetuses with defect of the mandible and fusion of the sternebrae[625]	10.0	17.5	Expected
	Increased incidences of foetuses with deformity of the vertebral column in the cervical and thoracic regions[625]	1.00	1.75	Expected
	Increased fused ribs[631]	2.43	4.25	Expected

Table X18-7: Relevant reproductive health endpoints for Dibutyltin oxide				
Group	**Effects seen**	**Threshold dose (mg/kg/ day) (no effects)**	**Converted Threshold dose (mg/ m^3) (no effects)**	**Effects in humans**
Embryonic/ foetal development	Increased mandible complications[631]	1.99	3.48	Expected
	Anomaly of mandibular fixation, cranial hypoplasia, and fused ribs[631]	1.99	3.48	Expected

Table X18-8: Relevant reproductive health endpoints for Dibutyltin diacetate				
Group	**Effects seen**	**Threshold dose (mg/kg/ day) (no effects)**	**Converted Threshold dose (mg/ m^3) (no effects)**	**Effects in humans**
Embryonic/ foetal development	Increased mandible complications[631]	2.81	4.92	Expected
	Anomaly of mandibular fixation, cranial hypoplasia, and fused ribs[631]	2.81	4.92	Expected

[631] Noda T, Morita S, Baba A. (1993). Toxicology, 85:2–3, 149-160, as cited in ECHA registration dossier for dibutyltin dilaurate

Table X18-9: Relevant reproductive health endpoints for Dibutyltin maleate				
Group	**Effects seen**	**Threshold dose (mg/kg/ day) (no effects)**	**Converted Threshold dose (mg/ m^3) (no effects)**	**Effects in humans**
Embryonic/ foetal development	Increased mandible complications[631]	2.78	4.87	Expected
	Anomaly of mandibular fixation, cranial hypoplasia, and fused ribs[631]	2.78	4.87	Expected

Table X18-10: Relevant reproductive health endpoints for Butyl(3-hydroxybutyl)tin dilaurate (3-OHDBTL)				
Group	**Effects seen**	**Threshold dose (mg/kg/ day) (no effects)**	**Converted Threshold dose (mg/ m^3) (no effects)**	**Effects in humans**
Embryonic/ foetal development	Increased mandible complications[631]	51.80	90.65	Expected
	Fused mandibula or micromandibula[631]	51.80	90.65	Expected

Other health endpoints

The purpose of this section is to list relevant effects other than reproductive toxicity. A number of non-reprotoxic maternal effects have been identified for Dibutyltin dichloride:

- Reduced adjusted weight gain during pregnancy (which referred to maternal body weight gain excluding the gravid uterus);
- Decreased mean weight of the thymus; and
- Decreased relative thymus weight of the females(P0).

X18.2.2 Summary of thresholds and DRRs

DRRs given below are expressed as % effect increase/mg/m^3 (TWA8). A result/number such as a negative DRR of 4.91 is showing negative response (decrease in effects). The DNELs for workers for organotins exposure range between 0.01 to 0.07 mg/m^3. All of the effects have thresholds greater than 0.07 mg/m^3.

Table X18-11: Selected Occupational endpoints: Thresholds and dose response for Dibutyltin dilaurate			
Effects	**Threshold**	**Dose response curve**	
	Converted (mg/m^3)	**Converted (mg/ m^3)**	**Slope (%/mg/ m^3)**
Increased mandible complications	8.84	79.5	No response hence no slope
Anomaly of mandibular fixation, cranial hypoplasia, and fused ribs	8.84	79.5	No response hence no slope

Table X18-12: Selected Occupational endpoints: Thresholds and dose response for Dibutyltin dichloride			
Effects	Threshold	Dose response curve	
	Converted (mg/ m³)	Converted (mg/ m³)	Slope (%/mg/ m³)
Higher number of non-pregnant females	6.65	6.65	4.71
Higher pre-implantation loss	6.65	6.65	4.74
Increased number of litters totally resorbed	13.3	13.3	5.17
Increased number of resorptions and dead foetuses per litter in early stage	6.65	6.65	30.08
Increased post-implantation loss per litter	0.67	5.99	16.47
Higher incidence of post-implantation loss per litter	8.75	4.4	No response hence no slope
Higher incidence of post-implantation loss per litter	1.75	15.8	No response hence no slope
Increased post-implantation loss	2.63	14.88	4.99
Decreased number of live foetuses per litter	6.65	6.65	-3.94
Increased Pup mortality (F1)	2.63	14.88	3.03
Higher number of resorptions and dead foetuses per litter	8.75	4.4	No response hence no slope
Increased incidence of totally resorbed litters	35	35	No response hence no slope
Increased incidence of litters totally resorbed	17.5	8.75	No response hence no slope
Decreased survival rate of foetuses at terminal caesarean sectioning	0.88	7.9	No response hence no slope
Decreased number of females with live-born pups	2.63	14.88	-4.48
Decreased number of pups delivered	2.63	14.88	-3.15
Decreased number of live-born pups	2.63	14.88	-6.06
Lower number of live foetuses per litter	8.75	4.4	No response hence no slope
Lower number of live foetuses per litter	1.75	15.8	No response hence no slope
Decreased placental weight	4.38	4.38	No response hence no slope
Pup weight decreased on PN 4 (F1)	2.63	14.88	-1.68
Decreased Gestation index	2.63	14.88	-3.83
Pup weight decreased on PN 1 (F1)	2.63	14.88	-1.44
Increased percentage of runts PN 1	2.63	14.88	4.98
Increased percentage of runts PN 4	2.63	14.88	2.41
Increased incidence of ovarian cysts in high-dose females	2.63	14.88	No response hence no slope
Decreased body weights of live foetuses	4.38	4.38	No response hence no slope
High incidence of foetuses with malformations (Cleft jaw and ankyloglossia were the most frequent malformations observed in the affected foetuses)	4.38	4.38	No response hence no slope
Increase in the incidence of foetuses with skeletal malformations	4.38	4.38	No response hence no slope
Increased incidence of foetuses with skeletal anomalies	3.5	31.5	No response hence no slope
Increase in the incidence of foetuses with skeletal malformations	3.5	31.5	No response hence no slope
Increased incidence of fused ribs and deformed vertebral column	4.38	4.38	No response hence no slope

Table X18-12: Selected Occupational endpoints: Thresholds and dose response for Dibutyltin dichloride			
Effects	Threshold	Dose response curve	
	Converted (mg/ m^3)	Converted (mg/ m^3)	Slope (%/mg/ m^3)
Increase in the incidence of foetuses with external malformations	3.5	31.5	No response hence no slope
Increase in the incidence of foetuses with external malformation	1.75	15.8	3.73
Higher incidence of foetuses with internal malformations	3.5	31.5	No response hence no slope
Increased incidence of foetuses with internal malformations	1.75	15.8	No response hence no slope
Increased mandible complications	4.25	38.3	No response hence no slope
Increased incidences of foetuses with defect of the mandible and fusion of the sternebrae	17.5	8.8	No response hence no slope
Increased incidences of foetuses with deformity of the vertebral column in the cervical and thoracic regions	1.75	15.8	No response hence no slope
Increased fused ribs	4.25	38.3	No response hence no slope

Table X18-13: Selected Occupational endpoints: Thresholds and dose response for Dibutyltin oxide			
Effects	Threshold	Dose response curve	
	Converted (mg/ m^3)	Converted (mg/ m^3)	Slope (%/mg/ m^3)
Increased mandible complications	3.48	3.48	No response hence no slope
Anomaly of mandibular fixation, cranial hypoplasia, and fused ribs	3.48	3.48	No response hence no slope

Table X18-14: Selected Occupational endpoints: Thresholds and dose response for Dibutyltin diacetate			
Effects	Threshold	Dose response curve	
	Converted (mg/ m^3)	Converted (mg/ m^3)	Slope (%/mg/ m^3)
Increased mandible complications	4.92	44.3	No response hence no slope
Anomaly of mandibular fixation, cranial hypoplasia, and fused ribs	4.92	44.3	No response hence no slope

Table X18-15: Selected Occupational endpoints: Thresholds and dose response for Dibutyltin maleate (DBTM; EC Number 201-077-5; CAS Number 78-04-6)			
Effects	Threshold	Dose response curve	
	Converted (mg/ m^3)	Converted (mg/ m^3)	Slope (%/mg/ m^3)
Increased mandible complications	4.87	43.8	No response hence no slope
Anomaly of mandibular fixation, cranial hypoplasia, and fused ribs	4.87	43.8	No response hence no slope

Table X18-16: Selected Occupational endpoints: Thresholds and dose response for Butyl(3-hydroxybutyl)tin dilaurate (3-OHDBTL)			
Effects	Threshold	Dose response curve	
	Converted (mg/ m^3)	Converted (mg/ m^3)	Slope (%/mg/ m^3)
Increased mandible complications	90.65	90.65	No response hence no slope
Fused mandibula or micromandibula	90.65	90.65	No response hence no slope

The following table summarises all effects retained for further analysis (i.e. for which effects were observed and DRRs could be derived). Effects that reflect the same underlying change are considered together. Each health effect has been assigned a monetizable effect correlate.

The upper limit is the limit of the interval across which one can extra/interpolate the slope. Above this limit one should not use the slope identified here. The slope is considered to hold constant between the threshold and upper limit.

Table X18-17: Summary of effects, thresholds and DRRs retained for further analysis				
Health effect	Threshold (mg/ m^3)	Slope (% effect change/mg/ m^3)	Upper limit (mg/ m^3)	Monetizable effect correlate
Higher number of non-pregnant females;	6.65	4.71	13.3	Impaired or reduced fertility men & women;
Higher pre-implantation loss;	6.65	4.74	13.3	Impaired or reduced fertility men & women;
Increased number of litters totally resorbed;	13.3	5.17	26.6	Spontaneous abortion or still birth;
Increased number of resorptions and dead foetuses per litter in early stage;	6.65	30.08	13.3	Spontaneous abortion or still birth;
Increased post-implantation loss per litter;	0.67	16.47	6.66	Spontaneous abortion or still birth;
Increased Pup mortality (F1);	2.63	3.03	17.51	No monetizable effect identified;
Pup weight decreased on PN 4 (F1);	2.63	-1.68	17.51	No monetizable effect correlate
Pup weight decreased on PN 1 (F1);	2.63	-1.44	17.51	Low birth weight
Increased percentage of runts PN 1;	2.63	4.98	17.51	Low birth weight
Increased percentage of runts PN 4	2.63	2.41	17.51	No monetizable effect correlate;
Increase in the incidence of foetuses with external malformation	1.75	3.73	17.55	Skeletal effects or abnormalities of the limbs

X18.3 Relevant sectors, uses, and operations

This section provides an overview of the relevant sectors, uses and activities in which occupational exposure to the selected organotin compounds may occur.

DRRs could only be derived for one of the five compounds, i.e. dibutyltin dichloride, and as a result, the number of cases of ill health due to occupational exposure to certain concentrations, can only be quantified for dibutyltin dichloride. That is why this section and the following section on exposed workforce will predominantly focus on the identification and estimation of data for this substance.

All five substances are REACH-registered:

- Dibutyltin dilaurate in the tonnage band 100 – 1,000 tonnes per annum, 11 active registrants;
- Dibutyltin dichloride in the tonnage band 10 – 100 tonnes per annum, 4 active registrants;
- 2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate in the tonnage band 1,000 – 10,000 tonnes per annum, 5 active registrants;
- Dibutyltin oxide in the tonnage band 1,000 – 10,000 per annum, 9 active registrants; and
- Dibutyltin bis(2-ethylhexanoate) in the tonnage band 10 - 100 tonnes per annum, 1 active registrant.

The number of manufacturers and importers (including companies that manufacture or import substances in amounts less than 1 ton per annum) can be estimated by the number of notifications listed in ECHA's C&L Inventory. Several companies can be associated with each notification. A total of 86 notifications (provided by 925 companies) were received for dibutyltin dilaurate; 14 notifications (provided by 85 companies) were received for dibutyltin dichloride; 10 notifications (provided by 166 companies) were received for 2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate; 27 notifications (provided by 434 companies) were received for dibutyltin oxide; and 12 notifications (provided by 90 companies) were received for Dibutyltin bis(2-ethylhexanoate). [632]

All five Organostannic compounds are listed in Annex I Part 1 of the Prior Informed Consent (PIC)[633] regulation under industrial chemicals for public use, and are subject to export notification procedure. PIC regulation places obligations on companies who wish to export these chemicals, mixtures or articles containing one or more chemicals listed in Annex I to non-EU countries. Data on the origin of exporter, the destination and number of notifications presented below.

Table X18-18: Number of export notifications, main EU exporters and non-EU importers of organotin compounds, since 2013

Chemical/Mixture/Article	Subtotal	2018	2017	2016	2015	2014	2013
Organotin compounds							
Dibutyltin compound	1	1	0	0	0	0	0
Dibutyltin compound preparation	77	22	27	28	0	0	0
Dibutyltin compounds preparation	19	19	0	0	0	0	0
dibutyltin compound preparation	2	1	1	0	0	0	0
Dibutyltin compound preparations are exported: -from Denmark to Iceland -from France to Serbia -from Germany to Argentina, China, Hong Kong, India, Indonesia, Kuwait, Malaysia, Philippines, Republic of Korea, Russian Federation, Serbia, South Africa, Switzerland, Thailand, Turkey, United States, -from the Netherlands to Australia, Japan, Russian Federation, Switzerland, United Arab Emirates -from Spain to Albania, Algeria, Brazil, Russian Federation, Serbia, Switzerland, Tunisia, Ukraine **Dibutyltin compounds preparations are exported:**							

[632] ECHA, 2018, "Summary of Classification and Labelling", available at: https://echa.europa.eu/information-on-chemicals/cl-inventory-database [accessed 31/07/2018]

[633] PIC regulation on ECHA, "List of chemicals Annex I", available at: https://echa.europa.eu/regulations/prior-informed-consent/list-chemicals

Table X18-18: Number of export notifications, main EU exporters and non-EU importers of organotin compounds, since 2013							
Chemical/Mixture/Article	**Subtotal**	**2018**	**2017**	**2016**	**2015**	**2014**	**2013**
-from France to Argentina, Australia, Chile, China, Colombia, India, Israel, Republic of Korea, Russian Federation, Serbia, South Africa, Switzerland, Tunisia, Ukraine, United States							
Dibutyltin dilaurate							
RX0771840025 DIBUTYLTINDILAURATE	3	1	1	1	0	0	0
dibutyltin dilaurate <1%	83	28	29	26	0	0	0
dibutyltin dilaurate 20-25%	11	3	4	4	0	0	0
Dibutyltin dilaurate is exported: -from Germany to Albania, Argentina, Australia, Brazil, Canada, China, Colombia, Ecuador, Egypt, Guatemala, Hong Kong, India, Indonesia, Islamic Republic of Iran, Israel, Japan, Jordan, Republic of Korea, Lao People's Democratic Republic, Lebanon, Malaysia, New Zealand, Pakistan, Peru, Philippines, Qatar, Russian Federation, Saudi Arabia, Singapore, Sri Lanka, South Africa, Switzerland, Taiwan, Thailand, Tunisia, Turkey, Ukraine, United Arab Emirate, United States -from the Netherlands to Egypt, Turkey, Israel, Saudi Arabia, South Africa, Switzerland, United Arab Emirates -from the United Kingdom to Hong Kong, India, Israel, Japan, Republic of Korea, South Africa, Taiwan, Turkey **Dibutyltin dilaurate of concentration <1% is exported:** -from Germany to Egypt and Saudi Arabia -from France to Canada, China, India, Indonesia, Malaysia, Republic of Moldova, Russian Federation, Switzerland, Turkey, Ukraine, United States -from Italy to China, India, Serbia, Switzerland, Thailand, Turkey **Dibutyltin dilaurate of concentration 20-25% is exported:** -from Italy to China, India, Japan, Republic of Korea							
Dibutyltin dichloride							
n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Dibutyltin dichloride is exported: -from Germany to China							
2-ethylhexyl 4,4-dibutyl-10-ethyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate							
2-ethylhexyl 4,4-dibutyl-10-ethyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate	2	1	0	1	0	0	0
2-ethylhexyl 4,4-dibutyl-10-ethyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate is exported: -from Germany to the Russian Federation							
Dibutyltin oxide							
Dibutyltin oxide	3	3	0	0	0	0	0
Dibutyltin oxide is exported: -from Germany to Australia, Brazil, India, Islamic Republic of Iran, Mexico, Switzerland, Taiwan, Turkey, United States -from the Netherlands to Egypt, Switzerland, Turkey, United Arab Emirates							
Dibutyltin bis(2-ethylhexanoate)							
No data available	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Sources: EPA[634]							

Dibutyltin dichloride is used in the following sectors:

[634] PIC regulation on ECHA, "Export Notifications", available at: https://echa.europa.eu/information-on-chemicals/pic/export-notifications?p_p_id=exportnotifications_WAR_echapicportlet&p_p_lifecycle=1&p_p_state=normal&p_p_mode=view&p_p_col_id=column-1&p_p_col_pos=2&p_p_col_count=3&_exportnotifications_WAR_echapicportlet_javax.portlet.action=search

Manufacture of chemical products (NACE C20):

Dibutyltin dichloride is produced by the reaction between tin tetrachloride (SnCl4) and a transalkylation agent. The final product is a mixture with monobutyltin trichloride (CAS No. 1118-46-3) and is distilled or recrystallized to purify. Dibutyltin dichloride is manufactured in a closed system to prevent moisture and air from it.[635]

Dibutyltin dichloride is also used as an intermediate in the manufacture of other chemical formulations. The sectors of their end use are:

- Scientific research and development; and
- Manufacture of bulk, large scale chemicals (including petroleum products).

Manufacture of rubber tyres and tubes (NACE C22.1.1):

Dibutyltin dichloride is used as an additive for the production of rubber tyres. The rubber used for the manufacture of tyre is a combination of natural and synthetic rubbers. Additives like dibutyltin dichloride are added to the synthetic rubber to modify them whereby the tin from DBTC forms a strong bond with carbon from the fillers such as carbon black that is used to improve the mechanical property of the synthetic rubber.[636]

The presence of dibutyltin dichloride at ≥ 0.1% by weight of tin in tyres for supply to and use by the general public is restricted from 1st of January 2012 according to the entry 20 of Annex XVII to REACH.

Other uses

In the past, dibutyltin dichloride has also been used to manufacture the following products[637]:

- Packaging, incl. food contact, credit cards;
- Rigid construction incl. foamed sheeting;
- Thin rigid film;
- Bottles;
- Pipes and mouldings;
- Profile extrusions (e.g. windows)
- Flooring;
- Wallcovering;
- Steel coating; and
- Misc. (e.g. T-shirt printing).

All of the above-mentioned uses are considered to be no longer relevant or not very common uses, since they are not included in the REACH registration dossier for dibutyltin dichloride. Moreover,

[635] OECD, 2006, "SIDS Initial Assessment Meeting (SIAM) 23", Jeju, South Korea, 17-20 October 2006, available at: http://webnet.oecd.org/hpv/ui/SIDS_Details.aspx?id=3c211d5f-afb4-4b0e-a9a0-ecbd9b2253ec

[636] Miyazaki, 2012, "Rubber Composition for Base Tread, and Pneumatic Tire". United States Patent, Pub. No.: US 2012/0053263 A1, available at: https://data.epo.org/publication-server/pdf-document?pn=2784115&ki=B1&cc=EP

[637] RAR, 2005, "Risk Assessment Studies on Targeted Consumer Applications of Certain Organotin Compounds", prepared for DG Enterprise and Industry by Risk & Policy Analysts Ltd (RPA), available at: https://ec.europa.eu/docsroom/documents/13041/attachments/1/translations/en/renditions/native

reviewed sources of information, which identified these as uses of dibutyltin dichloride are dated prior to 2012.

X18.3.1 Summary of sectors and uses

The sectors and uses where occupational exposure to dibutyltin dichloride can potentially take place are listed below.

Table X18-19: Dibutyltin dichloride – sectors, subsectors and uses/activities			
Sector	**Subsector**	**Uses/activities**	**NACE codes**
Manufacture of chemicals and chemical products	Manufacture of dibutyltin dichloride		C20
	Intermediate in the manufacture of other chemical formulations, including bulk, large scale chemicals (including petroleum products)		
Manufacture of rubber tyres and tubes	Additive for the production of rubber tyres		C22.11

X18.4 Exposed workforce

X18.4.1 Total number of exposed workers

Estimates identified through literature review and consultation for this study

No estimates of the number of workers exposed (or potentially exposed) to dibutyltin dichloride in the EU have been identified from published literature**.**

The potentially exposed workforce, can however, be estimated, for the purposes of this study, based on employment figures retrieved from Eurostat, and a number of assumptions based on the extent of dibutyltin dichloride application within the relevant sectors.

The assumptions made and numbers of workers potentially exposed to dibutyltin dichloride within each sector of use are listed below.

Table X18-20: Potentially exposed workforce in EU28 by sector			
Sector	**Uses and/or activities**	**Facts and *Assumptions***	**No of potentially exposed workers**
Manufacture of chemicals and chemical products (NACE C20)	Manufacture of dibutyltin dichloride	According to ECHA, Dibutyl dichloride is used in chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions. There are 4 registrants under REACH and 14 notifications (provided by 85 companies) are listed in ECHA's C&L Inventory, suggesting that 85 companies in the EU manufacture or import dibutyltin dichloride *Dibutyltin dichloride is used by 0.3% of companies in the chemicals sector*	*1,353 – 6,767*
	Intermediate in the manufacture of other chemical formulations, including bulk, large scale chemicals (including petroleum products)		

Table X18-20: Potentially exposed workforce in EU28 by sector			
Sector	**Uses and/or activities**	**Facts and *Assumptions***	**No of potentially exposed workers**
		0.1 – 0.5% of workers in subsectors specified above are exposed to dibutyltin dichloride	
Manufacture of rubber tyres and tubes (NACE C22.11)	Additive for the production of rubber tyres	Regarding manufacture of rubber tyres, exposure may occur since the compound is used at industrial sites, where it is used as an additive for the production of rubber tyres. ECHA says that an opportunity for exposure arises. During consultation, the International Institute of Synthetic Rubber Producers has indicated that the proportion of companies that use organotin compounds is small since they use them only to produce some specific types of rubber and only for certain synthetic rubber production technologies. Moreover, synthetic rubber producing plants are not labour-intensive plants. Most of the staff is male and between 20 and 60 years old. *0.1 – 0.5% of workers in this subsector are exposed to dibutyltin dichloride*	*124 - 621*
TOTAL	***1,477–7,388 of potentially exposed workers***		
Sources: The total numbers of employees and enterprises in each sector and the share of micro, small, medium and large enterprises have been retrieved from Eurostat; ECHA REACH and C&L inventory			

X18.4.2 Breakdown by gender and age

The breakdown of employees by age and gender is available on Eurostat only for 2-digit level NACE codes. The same share of workers will be applied to 3-digit level NACE codes (e.g. for NACE C22.11, the same share of female/male workers of reproductive age will be applied as for NACE C22).

Potentially exposed workers broken down by gender and reproductive age are presented below.

Table X18-21: Dibutyltin dichloride – potentially exposed workforce in EU28 broken down by gender & age						
Sector	**Subsector/uses**	**Total exposed workers**	**%M/%F**	**M/F**	**%M/%F of reproductive age***	**M/F reproductive age***
Manufacture of chemicals and chemical products (NACE C20)	Manufacture of dibutyltin dichloride	*1,353 – 6,767*	69%/31%	936 – 4,682/417-2,085	100%/74%	936 – 4,682/307 – 1,537
	Intermediate in the manufacture of other chemical formulations, including bulk, large scale					

Table X18-21: Dibutyltin dichloride – potentially exposed workforce in EU28 broken down by gender & age						
Sector	**Subsector/uses**	**Total exposed workers**	**%M/%F**	**M/F**	**%M/%F of reproductive age***	**M/F reproductive age***
	chemicals (including petroleum products)					
Manufacture of rubber tyres and tubes (NACE C22.11)	Additive for the production of rubber tyres	*124 - 621*	78%/22%	97 - 487/27-134	100%/88%	97 - 487/24 - 120
TOTAL	***1,033 – 5,169 of potentially exposed male workers of reproductive age*** ***331 – 1,657 of potentially exposed female workers of reproductive age***					
Sources: Eurostat – Labour Force Survey database and Structural Business Statistics database Note: *women aged 15-49 and men >15 are considered to be of reproductive age						

X18.4.3 Breakdown by member state

Table X18-22: Dibutyltin dichloride – MIN estimate of potentially exposed workforce of reproductive age by Member State and gender						
Member State	**Manufacture of chemicals C20**			**Manufacture of rubber tyres and tubes C22.11**		
	Total	**Males**	**Females**	**Total**	**Males**	**Females**
EU28	**1,243**	**936**	**307**	**121**	**97**	**24**
Belgium	45	35	10	2	2	0
Bulgaria	14	9	4	2	2	0
Czech Republic	34	26	8	7	5	2
Denmark	12	9	3	1	1	0
Germany	330	258	72	26	21	5
Estonia	:	:	:	:	:	:
Ireland	:	:	:	:	:	:
Greece	10	7	3	1	1	0
Spain	123	88	35	7	6	2
France	176	128	48	14	11	3
Croatia	:	:	:	1	1	0
Italy	145	111	34	14	11	3
Cyprus	:	:	:	:	:	:
Latvia	:	:	:	:	:	:
Lithuania	:	:	:	:	:	:
Luxembourg	:	:	:	:	:	:
Hungary	27	18	8	4	3	1
Malta	:	:	:	:	:	:
Netherlands	51	43	8	2	2	0
Austria	21	16	5	2	2	1
Poland	110	76	34	17	12	5
Portugal	:	:	:	2	1	1
Romania	:	:	:	:	:	:
Slovenia	7	5	2	1	1	0
Slovakia	14	11	3	3	2	1
Finland	12	9	3	1	1	0
Sweden	16	12	4	1	1	0

Table X18-22: Dibutyltin dichloride – MIN estimate of potentially exposed workforce of reproductive age by Member State and gender						
Member State	Manufacture of chemicals C20			Manufacture of rubber tyres and tubes C22.11		
	Total	Males	Females	Total	Males	Females
United Kingdom	93	72	21	10	8	2
Source: Eurostat and RPA analysis *: n/a*						

Table X18-23: Dibutyltin dichloride – MAX estimate of potentially exposed workforce of reproductive age by Member State and gender						
Member State	Manufacture of chemicals C20			Manufacture of rubber tyres and tubes C22.11		
	Total	Males	Females	Total	Males	Females
EU28	**6,219**	**4,682**	**1,537**	**607**	**487**	**120**
Belgium	223	174	49	9	8	1
Bulgaria	68	46	22	10	8	2
Czech Republic	170	129	40	37	24	12
Denmark	61	47	14	5	4	1
Germany	1,651	1,292	359	132	108	24
Estonia	:	:	:	:	:	:
Ireland	:	:	:	:	:	:
Greece	48	35	14	6	5	1
Spain	615	439	176	37	29	8
France	880	642	238	70	54	17
Croatia	:	:	:	4	4	1
Italy	727	556	171	71	56	15
Cyprus	:	:	:	:	:	:
Latvia	:	:	:	:	:	:
Lithuania	:	:	:	:	:	:
Luxembourg	:	:	:	:	:	:
Hungary	133	92	40	22	16	6
Malta	:	:	:	:	:	:
Netherlands	254	213	41	12	10	1
Austria	105	79	26	11	8	4
Poland	549	381	169	86	62	24
Portugal	:	:	:	10	7	3
Romania	:	:	:	:	:	:
Slovenia	37	27	10	6	5	1
Slovakia	72	55	17	16	10	6
Finland	60	46	15	4	4	1
Sweden	82	62	20	6	5	1
United Kingdom	465	358	107	52	43	9
Source: Eurostat and RPA analysis *: n/a*						

X18.4.4 Trends

Since 2012, a number of uses of dibutyltin dichloride have been restricted under REACH (for more information see Section X18.1.4 on legislation other than CAD). As a result, the number of exposed workers and exposure concentration (the REACH legislation has also set maximum allowed

concentrations of organotin compounds in certain products) has decreased. The number of exposed workers is expected to remain stagnant or continue decreasing very slightly in the future.

X18.4.5 Exposed workers: conclusion

The total number of potentially exposed workers is summarised below.

Table X18-24: Potentially exposed workforce: conclusion			
Estimate	**No of exposed workers**	**Men of reproductive age**	**Women of reproductive age**
Highest estimate	7,388	5,169	1,657
Lowest estimate	1,477	1,033	331
Estimate taken forward for modelling	4,433	3,101	994
Alternative estimate for the sensitivity analysis	-	-	-
Annual rate of change	-0.5%	-0.5%	-0.5%

X18.5 Exposure levels

X18.5.1 Exposure routes

The main exposure routes are inhalation and dermal absorption, exposure can also occur by oral route.

X18.5.2 Current exposure levels

No data on current exposure levels in occupational settings have been identified through the literature review.

Assumptions can be made based on the type of processes[638] dibutyltin dichloride is used in:

Manufacture of chemicals (NACE 20):

Manufacture of dibutyltin dichloride

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities; and
- PROC 15: Use as laboratory reagent.

Use as an intermediate:

[638] REACH registration dossier for dibutyltin dichloride – Intermediate use only, available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/24336/3/1/4
REACH registration dossier for dibutyltin dichloride – Full registration, available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14508

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions; and
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions.

Based on the PROC classifications relevant for dibutyltin dichloride specified in its REACH registration dossier, workers in the chemicals industry are likely to be exposed only to low concentrations of dibutyltin dichloride, mainly during PROC 3 and, to lesser extent, during PROC 8b and PROC 15.

Manufacture of rubber tyres and tubes (NACE 22.11):

- PROC 4: Chemical production where opportunity for exposure arises;
- PROC 5: Mixing or blending in batch processes;
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities;
- PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing); and
- PROC 14: Tabletting, compression, extrusion, pelletisation, granulation.

As interpreted from the description of above process categories (PROC 4, 5, 8b, 9, and 14), workers are at possible risk to dibutyltin dichloride exposure during its use as an additive for the production of rubber tyres.

X18.5.3 Trends

No information on measured occupational exposure concentrations is available. Since 2012, a number of uses of dibutyltin dichloride have been restricted under REACH (for more information see Section X18.1.4 on legislation other than CAD). As a result, the exposure concentrations (the REACH legislation has set maximum allowed concentrations of organotin compounds in certain products) has decreased.

X18.6 Current Risk Management Measures (RMMs)

Risk management measures that are recommended for reducing exposure (apart from the use of closed systems) specified in REACH registration dossiers for organotin compounds are listed below.

Table X18-25: Recommended RMMs for organotin compounds from REACH registrations

Substance	Measure	Details
Dibutyltin dilaurate; Dibutyltin dichloride; Dibutyltin bis (2-ethylhexanoate)	Organisational measures	Do not eat or drink at work; immediately remove contaminated clothing
	Respiratory protection	Gas filter type A if the occupational exposure limit or MAK value will be exceeded
	Eye protection	Safety glasses
	Skin and body protection	Chemical resistant protective clothing
	Hand protection	PVC or rubber protective gloves

Dibutyltin oxide	Organisational measures	Do not eat or drink at work; immediately remove contaminated clothing
	Respiratory protection	Particle filter FFP1 if the occupational exposure value or MAK value will be exceeded
	Eye protection	Safety glasses
	Skin and body protection	Chemical resistant protective clothing
	Hand protection	PVC or rubber protective gloves
2-ethylhexyl 10-ethyl-4,4-dicotyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate	Organisational measures	Appropriate exhaust ventilation at machinery; frequently monitor and control the working atmosphere
	Respiratory protection	Wear suitable respiratory equipment in the case of hazardous fumes
	Eye protection	Safety glasses
	Hand protection	PVC or neoprene gloves
Sources: ECHA (2018): Dibutyltin dilaurate REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14904/9 ECHA (2018): Dibutyltin dichloride REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14904/9 ECHA (2018): Dibutyltin oxide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14790/9 ECHA (2018): 2-ethylhexyl 10-ethyl-4,4-dicotyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/14171/9		

X18.7 Market analysis

Data on number and proportion of SMEs, average turnover per enterprise and R&D expenditure for sectors in which occupational exposure to dibutyltin dichloride occurs are summarized below.

X18.7.1 Number of SMEs in each sector

Table X18-26: Number and proportion of SMEs by size of enterprise and sector

Sector	TOTAL	Micro		Small		Medium		Large	
	No. firms	No. firms	% of total	No. firms	% of total	No. firms	% of total	No. firms	% of total
C20.1	**8,980**	5,190	58%	2,010	22%	980	11%	360	4%
C22.1	**7,690**	5,090	66%	1,740	23%	640	8%	230	3%
Source: Eurostat's Structural Business Statistics database									

X18.7.2 Average turnover by size of enterprise

Table X18-27: Average turnover by sector and size of enterprise, 2016

Sector	Micro			Small			Medium			Large		
	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m
C20.1	6,854	5,190	1.32	19,422	2,010	9.66	68,909	980	70.32	234,358	360	650.99

Table X18-27: Average turnover by sector and size of enterprise, 2016												
Sector	Micro			Small			Medium			Large		
	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m
C22.1	1,569	5,090	0.31	5,271	1,740	3.03	10,533	640	16.46	59,602	230	259.14
Source: Eurostat's Structural Business Statistics database												

X18.7.3 R&D expenditure

Table X18-28: Business expenditure on R&D per sector (in € million), EU28		
Sector	Data availability	R&D expenditure (in €m)
C20.1	C20	6,659.7
C22.1	C22	2,371
Source: Eurostat Notes: EU28 totals do not include data for some member states, due to confidentiality.		

X18.8 Burden of ill health

X18.8.1 Cases of ill health

To assess the potential cases of ill health, three exposure scenarios are considered:

- Member state OEL: most common OEL is 0.1 mg/m^3;
- 100 x DNEL (inhalation): 1 mg/m^3; and
- Highest value from exposure data: no occupational exposure data available

Endpoints considered (see Section X18.2 for detailed description of endpoint selection process):

Table X18-29: Selected endpoints relevant to exposure to dibutyltin dichloride				
Health effect	Threshold (mg/ m^3)	Slope (% effect change/mg/ m^3)	Upper limit (mg/ m^3)	Monetizable effect correlate
Higher number of non-pregnant females;	6.65	4.71	13.3	Impaired or reduced fertility men & women;
Higher pre-implantation loss;	6.65	4.74	13.3	Impaired or reduced fertility men & women;
Increased number of litters totally resorbed;	13.3	5.17	26.6	Spontaneous abortion or still birth;
Increased number of resorptions and dead foetuses per litter in early stage;	6.65	30.08	13.3	Spontaneous abortion or still birth;
Increased post-implantation loss per litter;	0.67	16.47	6.66	Spontaneous abortion or still birth;
Increased Pup mortality (F1);	2.63	3.03	17.51	No monetizable effect identified;
Pup weight decreased on PN 4 (F1);	2.63	-1.68	17.51	No monetizable effect correlate

Table X18-29: Selected endpoints relevant to exposure to dibutyltin dichloride				
Health effect	**Threshold (mg/ m^3)**	**Slope (% effect change/mg/ m^3)**	**Upper limit (mg/ m^3)**	**Monetizable effect correlate**
Pup weight decreased on PN 1 (F1);	2.63	-1.44	17.51	Low birth weight
Increased percentage of runts PN 1;	2.63	4.98	17.51	Low birth weight
Increased percentage of runts PN 4	2.63	2.41	17.51	No monetizable effect correlate;
Increase in the incidence of foetuses with external malformation	1.75	3.73	17.55	Skeletal effects or abnormalities of the limbs

OEL exposure scenario

The most common OEL, set by 19 out of 21 MS with binding OELs, is 0.1 mg/m^3.

If it is assumed that no workers (specifically female workers) are exposed to dibutyltin dichloride above this OEL, then no reproductive health effect occur in workers exposed to dibutyltin dichloride.

100x DNEL exposure scenario

100 x DNEL is 1 mg/m^3. Most thresholds for effects listed in above table lie below 1 mg/m^3, except for the threshold of 0.67 mg/m^3 for increased post-implantation loss per litter (i.e. spontaneous abortion or still birth).

If it is assumed that female workers are exposed to dibutyltin dichloride at 1 mg/m^3, then the only health effect that may occur is spontaneous abortion or still birth.

Highest value from exposure data scenario

No occupational exposure data have been identified for dibutyltin dichloride. This scenario cannot be modelled.

Summary

Table X18-30: Dibutyltin dichloride effects based on different exposure values				
Effect	**Thre-shold**	**DRR**	**Exposure scenario**	**Cases**
Spontaneous abortion or still birth	0.67	y=16.47x-11.03	OEL scenario: 0.1 mg/m^3	-
			100x DNEL scenario: 1 mg/m^3	5.4% of min. 26 and max. 215 = **1.43-11.63**
			exp scenario: n/a	-

331 to 1,657 female workers of reproductive age are potentially occupationally exposed to dibutyltin dichloride. 8-13% women normally experience spontaneous abortion or stillbirth, which applied to the numbers of female workers exposed to dibutyltin dichloride equals to min 26 and max 215**.** Assuming these workers were exposed to 100xDNEL (1mg/m^3), additional 5.4% of 26 - 215 female workers, i.e. 1.43 - 11.63, experienced spontaneous abortion or still birth due to this exposure.

Annex 19 Retinol

X19.1 Introduction

X19.1.1 Relevant substance(s)

The substances that have been selected for this study are retinol (EC No: 200-683-7 and CAS No: 68-26-8) and retinyl palmitate (EC No: 201-228-5 and CAS No: 79-81-2). [639]

These two substances are alternatively known as "Vitamin A" (CAS No: 11103-57-4 and EC No: 234-328-2). In fact, the term "Vitamin A" refers to a group of substances, the retinoids, including retinol and substances with similar structures with the biological characteristics of retinol (e.g. retinyl palmitate, retinyl acetate, retinyl linoleate etc.).

Vitamin A is a lipophilic-soluble Vitamin and as such a micronutrient essential for most of mammalian species. However, in general, undesirable effects can arise from both a lack of Vitamin A and Vitamin A hypervitaminosis. [640] Retinol and retinyl palmitate are known under a wide range of other chemical/trade names. A full list of alternative names can be found in the table below.

Table X19-1: Alternative names for retinol and retinyl palmitate

Type of name	Retinol	Retinyl palmitate
Chemical names	All-trans-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraen-1-ol	All-trans-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraene-1-yl palmitate
Trade names	Acon; Afaxin; Agiolan; Alphsterol; Epiteliol; Testavol	Arovit; Aquapalm; Aquasol A; Axerophthol palmitate; Dispatabs Tabs; Myvak; Myvax; Retinol palmitate (6CI, 7CI); Testavol S; Vitamin A Palmitate; Vitamin-A-Palmitat; Vitazyme A
Other Synonyms	All-trans-retinol; All-trans-retinyl-alcohol; Vitamin A alcohol; 15-apo-(3-caroten-15-ol); Axerol; Axerophthol; Axerophtholum; Biosterol; (E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-enyl)-2,4,6,8-nonatetraenol; (E)-3, 7-dimethyl-9-(2,6,6-trimethylcyclohexen-l-yl)-2,4,6,8-nonatetraenol; (E)-9-hydroxy-3,7-dimethyl-9-(2,6,6-trimethylcyclo-hexenyl)-1,3,5,7-Nonatetraene; OleoVitamin A; Retinol; Trans-retinol; 2-trans; 4-trans; Vitamin A; Vitamin A alcohol; Vitaminum A	All-trans-Retinyl palmitate; Retinyl palmitate; Palmitic acid; (E)-3,7-dimethyl-9-(2,6,6 trimethyl-cyclohexenyl)-2,4,6,8 nonatetraenyl ester; Palmitic acid retinyl ester; O-palmitoyl-all-trans-retinol; O-palmitoyl-retinol; Retinylpalmitate; 2-trans, 4-trans, 6-trans, 8-trans-retinylpalmitate; 2-trans, 4-trans, 6-trans, 8-trans-retinol palmitate; Retinol hexadecanoate; Trans-retinol palmitate; Trans-retinyl palmitate; RP
Sources: PubChem[641]; SCCS (2016)[640] and ECHA (2018)[639]		

The chemical formulas and chemical structures of retinol and retinyl palmitate are the following:

[639] ECHA, 2018, "Registered Substances database", available at: https://echa.europa.eu/information-on-chemicals/registered-substances [accessed 31/07/2018]

[640] Scientific Committee on Consumer Safety (SCCS), 2016, "Opinion on Vitamin A", SCCS/1576/16, available at: https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_199.pdf [accessed 31/07/2018]

[641] PubChem, 2018, "Retinol" and "Retinyl palmitate" available at: https://pubchem.ncbi.nlm.nih.gov/compound/retinol#section=Names-and-Identifiers and https://pubchem.ncbi.nlm.nih.gov/compound/5280531

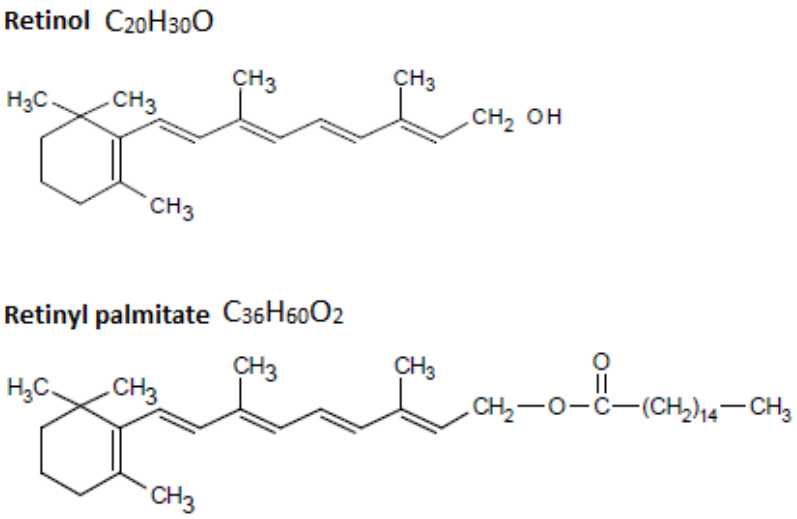


Figure X19-1: Retinol and retinyl palmitate– chemical structures
***Source*: *SCCS (2016)*[642]**

X19.1.2 Hazard classification(s)

Retinol has the following classifications[643]:

- Reproductive toxicity (**Repr. 1B**) - (Hazard Statement Code H360: May damage fertility or the unborn child);
- Serious eye irritation (**Eye Irrit. 2**) - (Hazard Statement Code H319: Causes serious eye irritation);
- Hazardous to the aquatic environment, long-term (chronic) (**Aquatic Chronic 4**) - (Hazard Statement Code H413: May cause long lasting harmful effects to aquatic life);
- Skin sensitization (**Skin Sens. 1**) - (Hazard Statement Code H317: May cause an allergic skin reaction);
- Acute toxicity (**Acute Tox. 4**) - (Hazard Statement Code H302: Harmful if swallowed);
- Reproductive toxicity (**Repr. 1A**) - (Hazard Statement Code H360: May damage fertility or the unborn child);
- Skin irritation (**Skin Irrit. 2**) - (Hazard Statement Code H315: Causes skin irritation); and
- Reproductive toxicity (**Repr. 2**) - (Hazard Statement Code H361: Suspected of damaging fertility or the unborn child).

[642] Scientific Committee on Consumer Safety (SCCS), 2016, "Opinion on Vitamin A", SCCS/1576/16, available at: https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_199.pdf [accessed 31/07/2018]

[643] ECHA, 2018, "Summary of Classification and Labelling - Retinol", available at: https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/119925 [accessed 31/07/2018]

The hazard classifications of retinyl palmitate are[644]:

- Reproductive toxicity (**Repr. 1B**) - (Hazard Statement Code H360: May damage fertility or the unborn child);
- Hazardous to the aquatic environment, long-term (chronic) (**Aquatic Chronic 4**) - (Hazard Statement Code H413: May cause long lasting harmful effects to aquatic life);
- Specific target organ toxicity - repeat exposure (**STOT RE 1**) - (Hazard Statement Code H372 Liver: Causes damage to organs through prolonged or repeated exposure);
- Hazardous to the aquatic environment, long-term (chronic) (**Aquatic Chronic 3**) - (Hazard Statement Code H412: Harmful to aquatic life with long lasting effects);
- Effects on or via *lactation* (**Lact.**) - (Hazard Statement Code H362: May cause harm to breast-fed children);
- Reproductive toxicity (**Repr. 1A**) - (Hazard Statement Code H360: May damage fertility or the unborn child);
- Skin irritation (**Skin Irrit. 2**) - (Hazard Statement Code H315: Causes skin irritation); and
- Reproductive toxicity (**Repr. 2**) - (Hazard Statement Code H361: Suspected of damaging fertility or the unborn child).

X19.1.3 Existing OELs and BLVs

There are no *Occupational Exposure Limits (OELs) or Biological Limit Values (BLVs)* set for retinol and retinyl palmitate in the EU. Similarly, no OELs are established for these substances in non-EU countries such as Canada, the US, Australia and Mexico. [645]

The DNELs (Derived No Effect Levels) are only available for retinyl palmitate[646] and are summarised below[647]:

- DNEL for workers via inhalation route
  - The occupational long term DNEL for worker inhalation hazard is set at **0.55 mg/m³** (8h); potential health effects: systemic effect; and
- DNEL for workers via skin contact
  - The occupational long term DNEL is set at **1.6 mg/kg bw/day**; potential health effects: systemic effects.

[644] ECHA, 2018, "Summary of Classification and Labelling – Retinyl palmitate", available at: https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/86754 [accessed 31/07/2018]

[645] Spectrum Chemical Mfg Corp, 2016, "Scientific Documentation, V1159", available at: http://healthdocbox.com/Cholesterol/76103935-Scientific-documentation-v1159-vitamin-a-palmitate-1-70-miu-g-usp.html [accessed 01/08/2018]

[646] ECHA, 2018, "Summary of Classification and Labelling – Retinyl palmitate", available at: https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/86754 [accessed 31/07/2018]; and
ECHA, 2018, "Summary of Classification and Labelling - Retinol", available at: https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/119925 [accessed 31/07/2018]

[647] Material Safety Data Sheet VITAMIN A PALMITATE https://www.aromantic.co.uk/technical-documents/msds/vitamin-a-palmitate-msds.aspx [accessed 10/08/2018]

X19.1.4 Legislation other than CAD

This section screens out the uses that are mentioned in literature but that are no longer relevant due to regulatory or voluntary phase outs.

No uses are restricted under REACH.

The use of Vitamin A in cosmetics products has been questioned by German and Norwegian authorities. German and Norwegian health agencies have raised a concern that daily skin application of vitamin A creams may contribute to excessive vitamin A intake for pregnant women and other populations. [648] In 2016, the European SCCS reviewed the use of vitamin A in body care products. It concluded that it would not restrict pre-formed vitamin A in cosmetics because it was unlikely that these products alone would expose consumers to harmful amounts. The committee noted that when added to the significant exposures from food, any additional source of exposure, including cosmetics products, may cause populations to exceed the upper intake levels (UL).[649]

With regard to national level restrictions, the use of retinol and retinyl esters in cosmetic products is restricted in the Norwegian cosmetics regulations with maximum allowed concentrations of 0.3% retinol and 0.7% retinyl palmitate.[650]

The use of retinol is also restricted in Canadian cosmetics with the maximum allowed concentrations of 1.0% retinol equivalents; 1.15% w/w retinyl acetate and 1.83% w/w retinyl palmitate. [651]

As defined by the Commission implementing regulation (EU) 2015/724[652], the authorisation of retinyl acetate, retinyl palmitate and retinyl propionate, as additives belonging to the additive category 'nutritional additives' and to the functional group 'vitamins, pro-vitamins and chemically well-defined substances having similar effect', is denied for use in water. Additionally, these substances are authorised as additives in animal nutrition subject to certain conditions. The regulation allows for a transitional period for interested parties to prepare themselves to meet the new requirements resulting from the authorisation. The transitional period ends May 26th 2025.

The following provisions on handling retinyl palmitate additives are already in place[652]:

- The additive shall be incorporated into the feed via a premixture;
- Retinyl palmitate may be placed on the market and used as an additive consisting of a preparation;
- For the content, as set out on the label, the following equivalency shall be used: 1IU = 0,5458 µg retinyl palmitate;

[648] EWG, 2018, "Retinol (Vitamin A)", *Cosmetics Database*, available at: https://www.ewg.org/skindeep/ingredient/706889/RETINOL_(VITAMIN_A)/# [accessed 06/08/2018]

[649] Scientific Committee on Consumer Safety (SCCS), 2016, "Opinion on Vitamin A", SCCS/1576/16, available at: https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_199.pdf [accessed 31/07/2018]

[650] VKM, 2012, "Risk assessment of vitamin A (retinol and retinyl esters) in cosmetics", available at: https://zenodo.org/record/827290#.W35UOrh9i00 [accessed 06/08/2018]

[651] Government of Canada, 2018, "Cosmetic Ingredient Hotlist - List of Ingredients that are Restricted for Use in Cosmetic Products", available at: https://www.canada.ca/en/health-canada/services/consumer-product-safety/cosmetics/cosmetic-ingredient-hotlist-prohibited-restricted-ingredients/hotlist.html#tbl2 [accessed 06/08/2018]

[652] (EU) 2015/724, "COMMISSION IMPLEMENTING REGULATION (EU) 2015/724 of 5 May 2015 concerning the authorisation of retinyl acetate, retinyl palmitate and retinyl propionate as feed additives for all animal species", available at: https://eur-lex.europa.eu/legal-content/SL/TXT/?uri=uriserv%3AOJ.L_.2015.115.01.0025.01.ENG

- The mixture of retinyl acetate, retinyl palmitate or retinyl propionate shall not exceed the maximum content for the relevant species and categories;
- In the directions for use of the additive and premixtures indicate storage and stability conditions; and
- For safety: breathing protection, safety glasses and gloves shall be worn during handling.

X19.2 Summary of health endpoints, thresholds & DRRs

X19.2.1 Relevant health endpoints

Relevant reproductive health endpoints

The reproductive effects, which have been deemed as potentially relevant to humans identified through literature review are summarised below.

Table X19-2: 2 Retinol (or ***Retinyl palmitate) – summary of health effects			
Health effect identified in literature	Fertility/ development?		
	Fer	Dev	Monetisable effect correlate
Increased malformations:*** significant differences in foot length, biparietal diameter, occipitofrontal diameter and head circumference		Dev	Skeletal effects or abnormalities of the limbs Low birth weight- includes hydrocephalus, bulging fontanelles and other congenital effects not separated out below
Forceful vomiting in neonates		Dev	This effect cannot be monetised
Forceful vomiting in infants		Dev	This effect cannot be monetised
Episode of bulging of the fontanelle		Dev	Low birth weight- includes hydrocephalus, bulging fontanelles and other congenital effects not separated out below
Sources: West et al (1992, 1999, 2011)[653]; Baqui et al (1995)[654]; Biesalski (1989)[655]; Rothman et al (1995)[656]; ECHA dossier for Retinol[657]			

[653] West et al, 1992, "Tolerance of young infants to a single, large dose of vitamin A: a randomized community trial in Nepal", available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2393418/pdf/bullwho00045-0047.pdf
West et al, 1999, "Double blind, cluster randomised trial of low dose supplementation with vitamin A or â carotene on mortality related to pregnancy in Nepal", available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC27760/pdf/570.pdf
West et al, 2011, "Effects of Vitamin A or Beta Carotene Supplementation on Pregnancy-Related Mortality and Infant Mortality in Rural Bangladesh", available at: https://jamanetwork.com/journals/jama/fullarticle/1161866

[654] Baqui et al, 1995, "Bulging fontanelle after supplementation with 25 000 IU of vitamin A in infancy using immunization contacts", available at: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1651-2227.1995.tb13781.x

[655] Biesalski, 1989, "Tolerable Upper Intake Levels for Vitamins and Minerals", available at: http://www.efsa.europa.eu/sites/default/files/efsa_rep/blobserver_assets/ndatolerableuil.pdf

[656] Rothman et al, 1995, "Teratogenicity of High Vitamin A Intake", available at: https://www.nejm.org/doi/pdf/10.1056/NEJM199511233332101

[657] ECHA dossier for Retinol, Unnamed publication, 2000, available at: https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/11075/7/9/3

Other health endpoints

The purpose of this section is to list relevant effects other than reproductive toxicity. A number of non-reprotoxic effects on the parents have been identified:

- Gestational maternal night blindness[658]; and
- Risk of hip fracture in postmenopausal women[659].

X19.2.2 Summary of thresholds and DRRs

The threshold for retinol uptake is 3000 IU per day or 3mg/day or 0.3 mg/m^3. All of the effects except night blindness have thresholds > 0.3 mg/m^3 (see table below).

Most workers in Europe will be near the maximum recommended intake of 3000 IU (=international units). Very little additional exposure needs to be added to exceed this threshold. In fact, 2.5% of the population has already a > 3000 IU uptake.

DRRs given below are expressed as % effect increase/mg/m^3 (TWA8). All dose-responses observed are of a similar magnitude, there are no outliers that would need to be eliminated. A result/number such as a negative DRR of 0.15 is showing negative response (decrease in effects).

Table X19-3: Selected endpoints: Thresholds and dose response for Retinol (or ***Retinyl palmitate)

Health Effects	Threshold	Dose response curve	
	Converted (mg/m^3)	Converted (mg/m^3)	Slope (%/mg/m^3)
Increased malformations: significant differences in foot length, biparietal diameter, occipitofrontal diameter and head circumference***	77	77	0.584
Forceful vomiting in neonates	2.80	25.2	-0.15
Forceful vomiting in infants	2.80	25.2	0.06
Episode of bulging of the fontanelle	0.70	6.30	1.27
Gestational maternal night blindness	0.007	0.063	-33.3
Risk of hip fracture in postmenopausal women	0.015	0.135	no slope

The effects retained for further analysis (e.g. number of cases of ill health as a result of occupational exposure to retinol or retinyl palmitate etc.) are highlighted in green. Forceful vomiting in neonates and infants as well as episode of bulging of the fontanelle will not be further considered as the study listing these as potential effects (i.e. West et al, 2011[660]) is irrelevant to occupational exposure. Gestational maternal night blindness and the risk of hip fracture in postmenopausal women have been excluded from further analysis, since these effects are non-reprotoxic.

[658] West et al, 2011, "Effects of Vitamin A or Beta Carotene Supplementation on Pregnancy-Related Mortality and Infant Mortality in Rural Bangladesh", available at: https://jamanetwork.com/journals/jama/fullarticle/1161866

[659] Feskanich et al, 2002, "Vitamin A Intake and Hip Fractures Among Postmenopausal Women", available at: https://jamanetwork.com/journals/jama/fullarticle/194525

[660] West et al, 2011, "Effects of Vitamin A or Beta Carotene Supplementation on Pregnancy-Related Mortality and Infant Mortality in Rural Bangladesh", available at: https://jamanetwork.com/journals/jama/fullarticle/1161866

X19.3 Relevant sectors, uses, and operations

This section provides an overview of the relevant sectors, uses and activities in which occupational exposure to retinol or retinyl palmitate may occur.

Both substances are REACH-registered, retinol in the in the tonnage band 0 - 10 tonnes per annum and retinyl palmitate in the tonnage band 100 – 1,000 tonnes per annum. 2 companies have submitted a joint registration in case of retinol and 4 companies have submitted a joint registration in case of retinyl palmitate.

The number of manufacturers and importers (including companies that manufacture or import substances in amounts less than 1 ton per annum) can be estimated by the number of notifications listed in ECHA's C&L Inventory. Several companies can be associated with each notification. A total of 9 notifications (provided by 213 companies) were received for retinol, suggesting that 211 companies manufacture or import less than 1 tonne of retinol per annum; and 27 notifications (provided by 450 companies) were received for retinyl palmitate, suggesting that 446 companies manufacture or import less than 1 tonne of retinyl palmitate per annum .[661]

In 2017, Agricultural Industries Confederation (AIC) issued a warning about a possible shortage expected of Vitamin A and Vitamin E, due to several incidents. The first: a fire during October in a German plant that produces a key precursor to production of Vitamin A and Vitamin E. The second: closure of a Chinese facility on environmental grounds. The Head of AIC's Feed Sector has stated that "*It would appear that normal volumes may not be produced until March or April 2018*".[662]

X19.3.1 Animal production, NACE A1.4

Vitamin A is used as an additive in the following forms of animal feed[663]:

- For pigs, chickens, turkeys, ducks, bovines and lambs for fattening;
- Other (pig, poultry and ruminant catefories);
- In a milk replacer for calves; and
- Fish feed and pet food.

The last category is more associated with consumer exposure rather than occupational.

Vitamin A is required in animals and essential for[662]:

- Vision;
- Growth differentiation and proliferation of a wide range of epithelial tissues;
- Bone growth; and
- Reproduction and embryonic development.

[661] Notified classification and labelling for retinol and retinol palmitate, available at: https://echa.europa.eu/hu/information-on-chemicals/cl-inventory-database/-/discli/details/119925 and https://echa.europa.eu/hu/information-on-chemicals/cl-inventory-database/-/discli/details/86754

[662] AllAboutFeed.com, 2017, "Possible shortage of vitamin A and E for feed", available at: https://www.allaboutfeed.net/Feed-Additives/Articles/2017/12/Possible-shortage-of-vitamin-A-and-E-for-feed-225191E/ [accessed 20/08/2018]

[663] EFSA, 2013, "Scientific Opinion on the safety and efficacy of vitamin A (retinyl acetate, retinyl palmitate and retinyl propionate) as a feed additive for all animal species and categories", available at: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2013.3037 *[accessed 10/08/2018]*

Vitamin A is included in the European Union Register of Feed Additives. It is authorised without a time limit in application of Article 9t (b) of Council Directive 70/524/EEC concerning additives in feedingstuffs for its use in all animal species as a nutritional additive.[663]

X19.3.2 Manufacture of food products, NACE C10

Vitamin A as retinol, retinyl acetate and retinyl palmitate (and beta-carotene) is authorised for use in food (Regulation (EC) No 1925/2006, amended by Regulation (EC) No 1170/2009) and in food supplements (Directive 2002/46/EC, Annex II), for addition for specific nutritional purposes in foods for particular nutritional uses (Regulation (EC) No 953/2009), and in processed cereal-based foods (baby foods for infants and young children) and juices but not in other baby foods (Directive 2006/125/EC, Annex IV), and it may be used (not the beta-carotene form) in infant formulae and follow-on formulae (Directive 2006/141/EC).[664]

Additionally, Vitamin A is added as a nutritional additive to various types of animal feeds.

Regarding the temporary shortage of Vitamin A caused by several incidents in 2017 (as mentioned in the previous subsection), Fefac, the European trade body for animal feed has warned that as stocks are not sufficient to offset the deficit of production, feed manufacturers globally will have no choice but to reduce the inclusion rates in feed. [662]

X19.3.3 Manufacture of chemicals, NACE 20 (in particular NACE 20.1 and 20.4)

Retinol, retinyl acetate, retinyl linoleate, retinyl palmitate and retinyl propionate are authorised in cosmetics as skin conditioners (Commission Decision 2006/257/EEC).[664]

Vitamin A is used as a cosmetic ingredient at maximum use concentrations of 0.05% (retinol equivalents) in body lotions, 0.3% (retinol equivalents) in hand and face creams as well as in other leave-on or rinse-off products. These products are usually presented as anti-wrinkle agents. In particular, retinol and its esters, mainly retinyl palmitates and acetates, are used in products such as face and eye creams, body lotions, sun lotions, lip products and baby creams, above all because of their anti-ageing effect. They induce biosynthesis of collagen in the skin and, at the same time, impede the UV-induced synthesis of collagen-reducing enzymes. These cosmetics promise to smooth wrinkles and fine lines in skin aged by both time and sun exposure. In toothpastes, Vitamin A serves to protect the gum epithelium against marginal parodontitis.[665]

X19.3.4 Manufacture of pharmaceuticals, NACE 21

Vitamin A is also listed as a pharmacologically active substance in veterinary medicinal products and it is not subject to maximum residue levels when used in food-producing animals (Commission Regulation (EC) No 37/2010).[664] Vitamin A is used in veterinary medicine only for short-term therapy in individual animals only for the treatment of Vitamin A deficiency. For instance, retinyl palmitate is an active ingredient in medicine products aimed for the prevention and treatment of vitamin

[664] EFSA, 2013, "Scientific Opinion on the safety and efficacy of vitamin A (retinyl acetate, retinyl palmitate and retinyl propionate) as a feed additive for all animal species and categories", available at: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2013.3037 *[accessed 10/08/2018]*

[665] Scientific Committee on Consumer Safety (SCCS), 2016, "Opinion on Vitamin A", SCCS/1576/16, available at: https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_199.pdf [accessed 31/07/2018]

deficiencies in horses, particularly during periods of illness, convalescence and general unthriftiness.[666]

Retinoid medicines are used mainly to treat conditions affecting the skin such as severe acne. Medicinal products contain higher concentrations of retinol than cosmetic products. However, there are uncertainties about the concentrations of retinol at which a cosmetic product is no longer considered cosmetic but rather medicinal. The Commission asked the opinion of the European Medicine Agency (EMA) to exclude the possibility that, at maximum use concentrations of 0.05% RE in body lotions, 0.3% RE in hand and face creams as well as in other leave-on or rinse-off products, Vitamin A could be considered a medicinal product instead of a cosmetic product. EMA replied that "locally applied products containing Vitamin A at the maximum concentrations of 0.05% (retinol equivalents) in body lotions, 0.3% (retinol equivalents) in hand and face creams as well as in other leave-on or rinse-off products, are not considered to be medicinal products by virtue of their function."[665]

X19.3.5 Summary of sectors and uses

The sectors and uses where occupational exposure can potentially take place are listed below.

Table X19-4: Retinol and retinyl palmitate – sectors, subsectors and uses/activities

Sector	Subsector	Uses/activities	NACE codes
Agriculture: Animal production	Additive in animal feed		A1.4
Manufacture of food products	Added for specific nutritional purposes to foods and food supplements		C10
	Added as a nutritional additive to various types of animal feeds		
Manufacture of chemicals (in particular basic chemicals and cosmetics)	Manufacture of retinol and retinyl palmitate		C20.1
	Manufacture of cosmetic products		C20.4
Manufacture of pharmaceutical products	Veterinary medicinal products and other medicinal products for the treatment of Vitamin A deficiency		C21
	Retinoid medicines (for severe acne treatment)		

X19.4 Exposed workforce.

X19.4.1 Total number of exposed workers

Estimates identified through literature review and consultation for this study

No estimates of the number of workers exposed (or potentially exposed) to retinol or retinyl palmitate in the EU have been identified from published literature and consultation.

The potentially exposed workforce, can however, be estimated, for the purposes of this study, based on employment figures retrieved from Eurostat, and a number of assumptions based on the extent of retinol and retinyl palmitate application within the relevant sectors.

[666] VDM Defra, 2011, "SUMMARY OF PRODUCT CHARACTERISTICS", available at: www.vmd.defra.gov.uk/productinformationdatabase/spc_documents/spc_339755.doc

The assumptions made and numbers of workers potentially exposed to retinol or retinol palmitate within each sector of use are listed below.

Table X19-5: Potentially exposed workforce in EU28 by sector			
Sector	**Uses and/or activities**	**Facts and *Assumptions***	**No of potentially exposed workers**
Agriculture: Animal production (NACE A1.4)	Additive in animal feed	There are 6.2m of agricultural holdings with livestock in the EU28 *Most of the agricultural holdings with livestock use feeds containing Vitamins A and E* *There is 1 worker (feeding operator) exposed per farm*	≈ *6.2m* (to be confirmed)
Manufacture of food products (NACE C10)	Added for specific nutritional purposes to foods and food supplements	European Food and Drink Industry Association has reported that 22% of companies (i.e. 58,160 in 2016) and 34% of workers in C10 (i.e. 1.57m in 2017) are involved in the manufacture of Grain mill and starch products, dairy products, drinks and other food products[667] *Vitamin A is added to food and drink products by 5-10% of companies* *1-5% of workers in subsectors specified above are exposed to retinol and retinyl palmitate*	*15,700 – 78,400*
	Added as a nutritional additive to various types of animal feeds	European Food and Drink Industry Association has reported that 2% of companies (i.e. 5,287 in 2016) and 3% of workers in C10 (i.e. 138,400 in 2017) are involved in animal feed manufacture[667] *Vitamin A is added to most types of animal feed as it is essential for good development of animals* *10-20% of workers in animal feed manufacture are exposed to retinol and retinyl palmitate*	*13,840 – 27,680*
Manufacture of chemicals (in particular basic chemicals NACE C20.1 and cosmetics NACE C20.4)	Manufacture of retinol and retinyl palmitate	According to ECHA's REACH and C&L inventory, there are 2 manufacturers or importers of retinol in the tonnage band 0 – 10 tonnes per annum and 211 manufacturers or importers of <1 tonne per annum and 2 manufacturers or importers of retinyl palmitate in the tonnage band of 100 – 1,000 tonnes per annum and 446 manufacturers or importers of <1 tonne per annum.	*200 - 980*

[667] Food and Drink Europe, 2015, "Data & Trends of the European Food and Drink Industry 2013-2014", pp 28

Table X19-5: Potentially exposed workforce in EU28 by sector			
Sector	**Uses and/or activities**	**Facts and *Assumptions***	**No of potentially exposed workers**
		The companies manufacturing or importing retinyl palmitate are manufacturing or importing retinol as well (the same companies are registered under REACH for both substances). *1-5% of workers at these companies are exposed to retinol or retinyl palmitate*	
	Manufacture of cosmetic products	There are 9,560 companies and 250,000 workers active in NACE C20.4 (Manufacture of soaps and detergents, cleaning and polishing preparations, perfumes and toilet preparations) *3% of companies in C20.4 are using retinol and retinyl palmitate in the manufacture cosmetic products* *1-5% of workers in this subsector are exposed to retinol or retinyl palmitate*	*2,500 – 12,500*
Manufacture of pharmaceutical products (NACE C21)	Veterinary medicinal products and other medicinal products for the treatment of Vitamin A deficiency	There are 4,560 companies and 573,000 workers active in NACE C21 *1% of companies in C20.4 are using retinol and retinyl palmitate in the manufacture cosmetic products*	*570 – 5,700*
	Retinoid medicines (for severe acne treatment)	*0.1-1% of workers in this subsector are exposed to retinol or retinyl palmitate*	
TOTAL	***6.23m – 6.33m of potentially exposed workers*** *(*the biggest contributor is Agriculture – animal production with 6.2m potentially exposed workers)*		
Sources: The total numbers of employees and enterprises in each sector and the share of micro, small, medium and large enterprises have been retrieved from Eurostat; Food and Drink Europe(2015); ECHA REACH and C&L inventory			

Breakdown by gender and age

The breakdown of employees by age and gender is available on Eurostat only for 2-digit level NACE codes. The same share of workers will be applied to 3-digit level NACE codes (e.g. for NACE C20.4, the same share of female/male workers of reproductive age will be applied as for NACE C20).

Potentially exposed workers broken down by gender and reproductive age are presented below.

Table X19-6: Retinol and retinyl palmitate – potentially exposed workforce in EU28 broken down by gender & age						
Sector	**Subsector/uses**	**Total exposed workers**	**%M/%F**	**M/F**	**%M/%F of reproductive age***	**M/F reproductive age***
Agriculture: Animal production (NACE A1.4)	Additive in animal feed	≈ *6.2m* (to be confirmed)	65%/35%	4m/2.2m	100%/55%	4m/1.2m
Manufacture of food products (NACE C10)	Added for specific nutritional purposes to foods and food supplements	*15,700 – 78,400*	56%/44%	8,740 – 43,650/6,960 – 34,740	100%/72%	8,740 – 43,650/4,980 – 24,920
	Added as a nutritional additive to various types of animal feeds	*13,840 – 27,680*	56%/44%	7,700 – 15,410/6,130 -12,270	100%/72%	7,700– 15,410/4,400 – 8,800
Manufacture of chemicals (in particular basic chemicals NACE C20.1 and cosmetics NACE C20.4)	Manufacture of retinol and retinyl palmitate	*200 - 980*	69%/31%	140 - 180/60 - 300	100%/74%	140 – 180/45 - 220
	Manufacture of cosmetic products	*2,500 – 12,500*	69%/31%	1,730 – 8,650/770 – 3,850	100%/74%	1,730 – 8,650/570 – 2,840
Manufacture of pharmaceutical products (NACE C21)	Veterinary medicinal products and other medicinal products for the treatment of Vitamin A deficiency	*570 – 5,700*	53%/47%	300 – 3,020/270 – 2,670	100%/77%	300 – 3,020/210 – 2,070
	Retinoid medicines (for severe acne treatment)					
TOTAL	***4.02m – 4.07m of potentially exposed male workers of reproductive age*** ***1.21m – 1.24m of potentially exposed female workers of reproductive age*** *(*the biggest contributor is Agriculture – animal production with 4m male and 1.2m female potentially exposed workers of reproductive age)*					
Sources: Eurostat – Labour Force Survey database and Structural Business Statistics database Note: *women aged 15-49 and men >15 are considered to be of reproductive age						

Trends

Exposure to retinol and retinyl palmitate remains more or less stagnant. Both the numbers of exposed workers and exposure concentrations are likely to decrease slightly in 2017 and 2018 due to an incident and resulting limited production at one of the main chemical manufacturing facilities in Germany.

Exposure to retinol and retinyl palmitate may decrease slightly in the future due to the implementation of regulation EU 2015/724, which sets new requirement for the use of 'vitamins, pro-vitamins and chemically well-defined substances having similar effect'. According to this regulation, the use of these substances is denied for use in water. Moreover, the use as additive in animal nutrition will be subject to additional conditions. The regulation allows for a transitional period, which ends May 26th 2025

X19.4.2 Exposed workers: conclusion

The total number of potentially exposed workers is summarised below.

Table X19-7: Potentially exposed workforce: conclusion			
Estimate	**No of exposed workers**	**Men of reproductive age**	**Women of reproductive age**
Highest estimate	6.33m (6.2m in agriculture)	4.07m (4m in agriculture)	1.21m (1.2m in agriculture)
Lowest estimate	6.23m (6.2m in agriculture)	4.02m (4m in agriculture)	1.24m (1.2m in agriculture)
Estimate taken forward for modelling m	6.28m	4.045m	1.225m
Alternative estimate for the sensitivity analysis	-	-	-
Annual rate of change	1%	1%	1%

X19.5 Exposure levels

X19.5.1 Exposure routes

The main exposure routes are dermal and oral absorption, exposure can also occur by inhalation.

X19.5.2 Current exposure levels

Only limited information on the current exposure levels in occupational setting is available. The exposure concentrations are generally assumed to be very low. However, it is important to note that most workers in Europe are near the maximum recommended intake of Vitamin A of 3000 IU (=international units, equals to 3mg/day or 0.3 mg/m^3). Very little additional occupational exposure needs to be added to exceed this threshold. In fact, 2.5% of the population has already a > 3000 IU uptake. Therefore, all calculations should take into account background exposure to 0.3 mg/m^3 as a 97.5% confidence interval.

The European Food Safety Authority ('the Authority') concluded in its opinion of 12 December 2012 that, under the proposed conditions of use in feed, retinyl acetate, retinyl palmitate and retinyl propionate do not have an adverse effect on animal health, human health or the environment.[668]

Potential exposure of users handling vitamin A in the formulation of food additives

[668] EFSA, 2013, "Scientific Opinion on the safety and efficacy of vitamin A (retinyl acetate, retinyl palmitate and retinyl propionate) as a feed additive for all animal species and categories", available at: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2013.3037 *[accessed 10/08/2018]*

There are different operations in a premixture factory during which the worker could be exposed to dust[664]:

- Taking the additive from its bag for weighing in the dispensary;
- Emptying bags of previously weighed material in the hopper or mixers; and
- Packing the final premixture.

Default values/positions for the calculation of potential exposure levels at premixture factories:

- A factory with a large throughput can prepare 40 premixture batches per day (8 hours per shift);
- The maximum time for weighing/emptying is 20 seconds;
- Total breathed air per worker of 10m^3 per 8 hours = 1.25 m^3 per hour;
- Percentage of premixtures that contain the additive: 100 %;
- Dusting potential measured: worst case 2.77 g/m^3; and
- Concentration of the active substance in dust: 151 710 IU/g dust (45.5 mg/g dust).

Calculation of exposure by inhalation during a working day:

- Batches with potential exposure → 40 (batches) × 1 (fraction of batches containing additive) = 40 (batches);
- Time of exposure → 40 × 20 seconds = 800 seconds;
- Inhaled air during exposure (Ia), m^3 → 1.25 m^3 per hour × 2 × 800/60/60 in hours = 0.55;
- Active substance in air (Asa), g/m^3→ 2.77 (dust in g/m^3) × 45.5 = 126 mg/m^3;
- Active substance inhaled (Asi), mg/day → 126 (Asa) × 0.55 (Ia) × 1 000 = 69; and
- Reduced by filter mask (Asir), mg/day → 69 (Asi) × 0.1 (by mask type P2) = 6.9 mg (22 997 IU).

Assuming that 10 m^3 air is inhaled during an 8-h workday[669], the workers can potentially be exposed to 6.9 mg/m^3 TWA of Vitamin A by inhalation (or to lower values, e.g. 0.69mg/m^3 if personal protection equipment, such as a filter mask is used).

Exposure concentrations in other sectors are unknown, and cannot even be estimated based on occupational exposure limit values (OELs) since there are no OELs for retinol or retinyl palmitate currently in place.

X19.5.3 Trends

No information on exposure trends is available. However, as noted in the previous section on the number of occupationally exposed workers, exposure to retinol and retinyl palmitate is likely to decrease slightly in 2017 and 2018 due to an incident and resulting limited production at one of the main chemical manufacturing facilities in Germany. Fefac, the European trade body for animal feed has warned that as stocks are not sufficient to offset the deficit of production, feed manufacturers globally will have no choice but to reduce the inclusion rates in feed. [662]

[669] SCOEL, 2009, "Recommendation from the Scientific Committee on Occupational Exposure Limits", available at: www.ec.europa.eu/social/BlobServlet?docId=6408&langId=en

X19.6 Current Risk Management Measures (RMMs)

X19.6.1 Overview of RMMs

Risk management measures that are recommended for reducing exposure (apart from the use of closed systems) specified in REACH registration dossiers for retinol and retinyl palmitate are listed below. The measures are the same for both retinol and retinyl palmitate.

Table X19-8: Retinol and retinyl palmitate REACH protective measures	
Measure	**Details**
Retinol and retinyl palmitate	
Respiratory protection	Respiratory protection in case of vapour/aerosol release. Particle filter with medium efficiency for solid and liquid particles (e.g. EN 143 or 149, Type P2 or FFP2)
Hand protection	Suitable chemical resistant safety gloves (EN 374) also with prolonged, direct contact (Recommended: Protective index 6, corresponding > 480 minutes of permeation time according to EN 374): E.g. nitrile rubber (0.4 mm), chloroprene rubber (0.5 mm), butyl rubber (0.7 mm) and other
Eye protection	Safety glasses with side-shields (frame goggles) (e.g. EN 166)
Body protection	Body protection must be chosen depending on activity and possible exposure, e.g. apron, protecting boots, chemical-protection suit (according to EN 14605 in case of splashes or EN ISO 13982 in case of dust)
General hygiene and safety measures	Under no circumstances should the product come into contact with the skin of pregnant women or be inhaled by them. Handle in accordance with good industrial hygiene and safety practice.
Source: ECHA (2018): Retinol and retinyl palmitate REACH registration dossier. Available at: https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/11075/9 and https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/13687/9	

X19.7 Market analysis

X19.7.1 Number of SMEs in each sector

Table X19-9: Number and proportion of SMEs by size of enterprise and sector									
Sector	**TOTAL**	**Micro**		**Small**		**Medium**		**Large**	
	No. firms	**No. firms**	**% of total**	**No. firms**	**% of total**	**No. firms**	**% of total**	**No. firms**	**% of total**
A1.4	-	-	-	-	-	-	-	-	-
C10	**264,350**	207,260	78%	44,540	17%	10,160	4%	2,400	1%
C20.1	**8,980**	5,190	58%	2,010	22%	980	11%	360	4%
C20.4	**9,560**	7,090	74%	1,600	17%	680	7%	170	2%
C21	**4,560**	2,240	49%	960	21%	820	18%	540	12%
Source: Eurostat's Structural Business Statistics database									

X19.7.2 Average turnover by size of enterprise

Table X19-10: Average turnover by sector and size of enterprise, 2016												
Sector	Micro			Small			Medium			Large		
	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m
A1.4	-	-	-	-	-	-	-	-	-	-	-	-
C10	57,030	207,260	0.28	140,842	44,540	3.16	273,000	10,160	26.87	490,000	2,400	204.17
C20.1	6,854	5,190	1.32	19,422	2,010	9.66	68,909	980	70.32	234,358	360	650.99
C20.4	2,315	7,090	0.33	5,848	1,600	3.66	17,418	680	25.61	47,164	170	277.44
C21	3,682	2,240	1.64	8,768	960	9.13	26,346	820	32.13	230,936	540	427.66
Source: Eurostat's Structural Business Statistics database												

X19.7.3 R&D expenditure

Table X19-11: Business expenditure on R&D per sector (in € million), EU28		
Sector	Data availability	R&D expenditure (in €m)
A1.4	A	520.3
C10	C10+C11	1,258.3
C20.1	C20	6,659.7
C20.4	C20	6,659.7
C21	C21	9,958.9
Source: Eurostat Notes: EU28 totals do not include data for some member states, due to confidentiality.		

X19.8 Burden of ill health

X19.8.1 Cases of ill health

To assess the potential cases of ill health, three exposure scenarios are considered:

- Member state OEL: no OELs in place;
- 100 x DNEL (inhalation): 55 mg/m^3; and
- Highest value from exposure data: 7.2 mg/m^3 (i.e. 6.9 mg/m^3 during formulation of food additives + background exposure of 0.3 mg/m^3).

Endpoints considered (see Section X19.2 for detailed description of endpoint selection process):

Table X19-12: Selected endpoints: Thresholds and dose response for Retinol (or ***Retinyl palmitate)				
Monetisable effects	Health Effects	Threshold	Dose response curve	
		Converted (mg/m^3)	Converted (mg/m^3)	Slope ($\%/mg/m^3$)
Skeletal effects or abnormalities of the limbs Low birth weight- includes hydrocephalus, bulging fontanelles and other congenital effects not separated out below	Increased malformations: significant differences in foot length, biparietal diameter, occipitofrontal diameter and head circumference***	77	77	0.584

OEL exposure scenario

This scenario cannot be modelled for retinol and retinyl palmitate since there are no OELs in place.

100x DNEL exposure scenario

100 x DNEL of 55 mg/m^3 is below endpoint threshold. There are no cases of ill health due to occupational exposure to retinol or retinyl palmitate.

Highest value from exposure data scenario

If the highest value from the evidence of occupational exposure to retinol and retinyl palmitate is used, i.e. 7.2 mg/m^3 (= 6.9 mg/m^3 during formulation of food additives + background exposure of 0.3 mg/m^3), it is still below the threshold of 77 mg/m^3, and therefore, it is assumed that no workers are exposed to retinol and retinyl palmitate above this level.

Summary

Table X19-13: Retinol and retinyl palmitate effects based on different exposure values.				
Effect	Thre-shold	DRR	Exposure scenario	Cases
Skeletal effects or abnormalities of the limbs Low birth weight- includes hydrocephalus, bulging fontanelles and other congenital effects not separated out below	77	y=0.584x-77	OEL scenario: no OELs	Cannot be quantified
			100x DNEL scenario: 55 mg/m^3	0
			Retinol and retinyl palmitate exp scenario: 7.2 mg/m^3	0

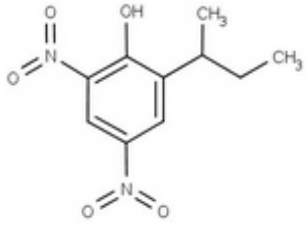
Annex 20 Dinoseb

X20.1 Introduction to dinoseb

X20.1.1 Relevant substance

Dinoseb has been used as a phenolic herbicide used on soybeans, vegetables, fruits and nuts, citrus, and other field crops for the selective control of grass and broadleaf weeds. It has been also used as an insecticide on grapes, and as a seed crop drying agent.[670] The substance was banned for use as a pesticide in the EU in 1991. Dinoseb and its salts and esters, under Annex III of the Stockholm Convention are severely restricted or banned for use as a pesticide.

Dinoseb is currently used as a process regulator for polymerisation processes and is used for this purpose in the manufacture of bulk, large scale chemicals (including petroleum products) and in the manufacture of plastics products, including compounding and conversion. The substance is registered under REACH in the 1000 to 10,000 tonnage band. The substance is an orange-brown viscous liquid or orange-brown solid with a pungent odour. The pure crystals are orange in colour.[671]

Table X20-1: Dinoseb substance information	
Substance Name	Dinoseb
Chemical formula	$C_{10}H_{12}N_2O_5$
Acronyms	2-*sec*-Butyl-4,6-dinitrophenol 2,4-Dinitro-sec-butylphenol (DNBP)
EC Number	201-861-7
CAS number	88-85-7
Structural formula	
Source: ECHA (2018): Dinoseb Substance Information. Available at: https://echa.europa.eu/substance-information/-/substanceinfo/100.001.692	

X20.1.2 Hazard classification(s)

Dinoseb is classified as a Repr.1B substance with a hazard statement code of H360Df (CLH). This means the substance may damage the unborn child and is suspected of damaging fertility.

Other hazard classifications of dinoseb (CLH) are:

- Acute Tox. 3 (H301): Toxic if swallowed;
- Acute Tox. 3 (H311): Toxic in contact with skin;
- Eye Irrit. 2 (H319): Causes serious eye irritation;

[670] EXTOXNET (1996): Dinoseb. Available at: http://extoxnet.orst.edu/pips/dinoseb.htm

[671] PubChem (2018): Dinoseb Experimental Properties. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/dinoseb#section=Computed-Properties

- Aquatic Acute 1 (H400): Very toxic to aquatic life; and
- Aquatic Chronic 1 (H410): Very toxic to aquatic life with long lasting effects

X20.1.3 Existing OELs and BLVs

Only one Member State has an OEL for dinoseb. Romania has an OEL of 0.1 mg/m^3 for dinoseb and a STEL of 0.5 mg/m^3. There are no BLVs for dinoseb in member states.

DNEL (Derived No Effect Level)

The Derived No Effect Levels (DNEL) for occupational dermal exposure is as follows:[672]

- The DNEL for long term occupational dermal exposure is 0.006 mg/kg bw/day, including overall assessment factor of 180 rated for developmental toxicity/teratogenicity; and
- The DNEL for short term occupational dermal exposure is 0.03 mg/kg bw/day, including overall assessment factor of 30 rated for developmental toxicity/teratogenicity.

The DNEL for occupational inhalation exposure are as follows: [672]

- The DNEL for long term occupational inhalation exposure is 0.04 mg/m^3, including an overall assessment factor of 12.5. and
- The DNEL for short term occupational inhalation exposure is 0.21 mg/m^3, including an overall assessment factor of 12.5.

. The short term inhalation DNEL for reproductive effects is 0.21 mg/m^3. If chronic exposure levels do not exceed 0.04 mg/m^3 and excursions do not exceed 0.21 mg/m^3, workers would be protected against reproductive effects. There is also currently no DNEL for carcinogenicity for long-term dermal exposure.

X20.1.4 Legislation other than CAD

REACH measures

Candidate list

Dinoseb has been included on the REACH candidate list for substances of very high concern (SVHC) under Article 57 as it is toxic for reproduction (Article 57(c)).[673]

Other Regulations

Rotterdam Convention

The use of Dinoseb and its salts and esters are listed on Annex III (banned or severely restricted pesticides) of the Convention.[674] The substance is subject to PIC under the Rotterdam Convention for

[672] ECHA (2018): REACH registration dossier for dinoseb. Available at: https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/12446/7/1

[673] ECHA (2018): Candidate List of substances of very high concern for Authorisation- Dinoseb. Available at https://echa.europa.eu/candidate-list-table/-/dislist/details/0b0236e1807de543

[674] Rotterdam Convention (2010): Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade. Available at:

hazardous substances. PIC is a mechanism for obtaining and disseminating decision of imported parties and also for ensuring compliance with these decisions by the exporting parties.[675] The United Kingdom is the only member state with export notifications.

Dinoseb previously was used as a pesticide; however the substance and its acetate and salts are now banned for use as pesticides in the EU.[676]

Acceptable Daily Intake (ADI)

Health Canada have derived an acceptable daily intake (ADI) as 0.001 mg/kg bw per day. The MAC (maximum acceptable concentration) for dinoseb in drinking water has been calculated as 0.01 mg/L.[677] US EPA has derived an oral Reference dose of 0.001 mg/kg bw/day, based on a reproductive LEL of 1 mg/kg/day. An uncertainty factor of 1000 was applied to account for uncertainties in the extrapolation from laboratory animals to humans (factor of 100), as well as concern for the lack of a no observed effect level (NOEL) in the reproduction study (factor of 10).[678]

X20.2 Summary of health endpoints, thresholds & DRRs

X20.2.1 Relevant health endpoints

Relevant reproductive health endpoints

Literature review has been undertaken to determine the relevant reproductive health endpoints for exposure to dinoseb. Those effects identified that have been deemed to be potentially relevant to humans are listed in the following table. These effects have also been grouped into the following groups along with their threshold doses:

- Production of germ cells/libido;
- Fertilisation/implantation;
- Embroynic/foetal development; and
- Childhood/lactation

http://www.pic.int/TheConvention/Overview/TextoftheConvention/RotterdamConventionText/tabid/1160/language/en-US/Default.aspx

[675] Rotterdam Convention (2010): The Prior Informed Consent (PIC) Procedure. Available at: http://www.pic.int/Procedures/PICProcedure/tabid/1364/language/en-US/Default.aspx

[676] European Commission (2016): EU Pesticides Database- Dinoseb, its acetate and salts. Available at: http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.detail&language=DE&selectedID=1256

[677] MAC= ((0.001 mg/kg bw/day*70 kg*0.20)/(1.5 L/day)) where ADI = 0.001 mg/kg bw/day, 70 kg= average weight of an adult, 0.2 is the proportion of daily intake of dinoseb allocated to drinking water and 1.5 L/day is the average daily consumption of drinking water for an adult.

[678] Dinoseb, CASRN 88-85-7, Integrated Risk Information System (IRIS) Chemical Assessment Summary; U.S. Environmental Protection Agency National Center for Environmental Assessment (1987).

Table X20-2: Dinoseb- summary of effects				
Group	**Effects seen**	**Threshold dose (mg/kg/ day or mg/ m³) (no effects)**	**Converted Threshold dose (mg/ m³) (no effects)**	**Effects in humans**
Production of germ cells/libido	Increase in motile sperm rate[679]	2.33	4.08	Expected
	Increase in abnormal sperm [679]	2.33	4.08	Expected
	Increase in abnormal sperm tail[679]	2.33	4.08	Expected
	Increase in abnormal sperm head[679]	2.33	4.08	Expected
	Decrease in live pups per litter[679]	2.33	4.08	Expected
	Decrease in epididymides weight**[680]	15.6	27.3	Expected
	Decrease in seminal vesicles weight**[680]	15.6	27.3	Expected
	Decrease in prostate weight[680]	15.6	27.3	Expected
	Decrease in testes weight **[680]	15.6	27.3	Expected
	Decrease in epididymal sperm count[680]	15.6	27.3	Expected
	Oligospermia[680]	9.10	15.9	Expected
	Abnormal sperm[680]	9.10	15.9	Expected
	Decreased fertility index for 0-14 days post-treatment mating period[680]	9.10	15.9	Expected
	Decreased fertility index for 104-112 days post-treatment mating period[680]	9.10	15.9	Expected
Fertilisation/ implantation	Decrease in gonadal weights to bodyweight ratio[681]	3.00	5.25	Expected
	Decreased mean number of corpora lutea per dam in F0 generation*[682]	3.00	5.25	Expected
	Decrease in mean number of pups born in F3 generation*[682]	3.00	5.25	Expected

[679] Matsumoto M et al (2008): Combined repeated dose and reproductive/developmental toxicity screening test of the nitrophenolic herbicide dinoseb, 2-sec-butyl-4,6-dinitrophenol, in rats Environ Toxicol., 23(2), pp 169-83. As cited in OECD SIDS report, 2007 on page no. 1&2. Note: the secondary reference cites these as increases although the opposite might be expected, similarly the decreases cited might have to be increases instead of decreases. Available at: https://hpvchemicals.oecd.org/UI/handler.axd?id=bc26a1c2-5c7d-403a-8deb-d6fa3a3dfa10

[680] Linder R.E. et al (1982): Testicular Effects of Dinoseb in Rats. Arch. Environm. Contam Toxicol., 11. Pp 475 - As cited in ECHA dossier for Dinoseb. Available at: https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/12446/7/9/2/?documentUUID=8542ca06-c426-4cc8-ba8b-22cc8d29766f

[681] Dow Chemical Company (1981a): MRID No. 00152675 as cited in US EPA IRIS, 1987 on page no. 02. Available at: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0047_summary.pdf

[682] ECHA Dossier for Dinoseb; Unnamed report 1981 and Unnamed report 1985. https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/12446/7/9/2/?documentUUID=641296ef-04ff-402b-b5db-43e552644444

Table X20-2: Dinoseb- summary of effects				
Group	**Effects seen**	**Threshold dose (mg/kg/ day or mg/ m³) (no effects)**	**Converted Threshold dose (mg/ m³) (no effects)**	**Effects in humans**
	Dead and resorbed foetuses[683]	3.00	8.75	Expected
	Decrease in % of embryo survival rate per litter at Day 12[684]	9.23	16.2	Expected
	Decrease in percentage of foetal survival rate per litter at birth[684]	6.90	12.1	Expected
Embryonic/ foetal development	Decrease in pup weight[681,682]	3.00	5.25	Expected
	Hydrocephaly, anophthalmia[683]	1.00	2.92	Expected
	Cleft palate, microcephaly, microphthalmia[683]	3.00	8.75	Expected
	Reduced foetal birth weight per litter[684]	9.23	16.2	Expected
	Decrease in foetal weight[685]	10.0	17.5	Expected
	Delayed ossification[685]	10.0	17.5	Expected
	Foetal skeletal variations[685]	5.00	8.75	Expected
	Decrease in foetal weight[685]	1.50	2.63	Expected
	Foetuses with microphthalmia[685]	1.50	2.63	Expected
	Decrease in foetal weight[686]	6.30	11.0	Expected
	Decrease in foetal crown-rump length[686]	8.00	14.0	Expected
	Delayed ossification[685]	1.50	2.63	Expected
	Foetus with hydronephrosis[685]	1.50	2.63	Expected
Childbirth/ lactation	Reduced body weight on postpartum day 1[686]	8.00	14.0	Expected
	Reduced body weight on postpartum day 7[686]	8.00	14.0	Expected

[683] Johnson, E. M., Bellet, E.M., Christian, M.S. and Hoberman, A.M. (1988). The hazard identification and animal NOEL phases of developmental toxicity risk estimation: a case study employing dinoseb. Advances in Modern Environmental Toxicology 15. 123-132 as cited in Matsumoto M et al, 2011. Developmental Toxicity of Nitrophenolic Herbicide Dinoseb, 2-sec-butyl-4, 6-dinitrophenol on page no 545. https://www.intechopen.com/download/pdf/12603

[684] Spencer. F et al (1982): Reproductive Toxicity in Pseudopregnant and Pregnant Rats following Postimplantational Exposure: Effects of the Herbicide Dinoseb as cited in ECHA Dossier for Dinoseb. https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/12446/7/9/2/?documentUUID=e0302341-19eb-4f5c-9ca5-b978e4dde5b4

[685] Giavini E et al (1986): Effect of method of administration on the teratogenicity of dinoseb in the rat Arch. Environ. Contam. Toxicol. 15, pp 377-384. As cited in ECHA dossier of Dinoseb. https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/12446/7/9/3/?documentUUID=ab4e6fd9-2929-4853-82e1-8fdb5af0b85e

[686] McCormack KM et al (1980): .Postnatal morphology and functional capacity of the kidney following prenatal treatment with dinoseb in rats. Journal of Toxicology and Environmental Health, Part A Current Issues, 6(3), pp633-43. As cited in ECHA dossier for Dinoseb. https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/12446/7/9/3/?documentUUID=a8e8bab6-3d51-4aba-ad5a-25132743d308

Table X20-2: Dinoseb- summary of effects				
Group	Effects seen	Threshold dose (mg/kg/ day or mg/ m^3) (no effects)	Converted Threshold dose (mg/ m^3) (no effects)	Effects in humans
*Attributed to decreased maternal weight ** Absolute weights only				

Other health endpoints

Dinoseb has a number of other health endpoints apart from reproductive effects. The substance is toxic to humans (CLH classification of Acute Tox. 3) and it is believed to act by uncoupling oxidative phosphorylation.[687]

Acute poisoning by dinoseb can result in vomiting, pain and swelling of the eyes, deteriorated vision, headache, malaise, lassitude, sweating, anorexia, pain in the chest and abdomen, excessive thirst, insomnia, loss of weight, generalized yellow staining of the skin and shortness of breath. Personality changes in affected individuals have also been documented. The accident exposure to dinoseb has led to death for one farm worker who sprayed dinoseb and dinitro-orth-cresol.[688]

The long term effects from dinoseb exposure for humans have not been discussed in the literature.

X20.2.2 Summary of thresholds and DRRs

The DRRs have been derived in accordance with the methodology presented in Annex 1. For those effects, where an effect has been observed (i.e. there is a slope in the dose-response curve) are presented in the following table.

[687] US EPA (1986): Pesticide fact sheet for Dinoseb, Fact sheet number 130.

[688] Heyndrickx A et al (1964): Fatal intoxication by man due to dinitro-ortho-cresol (DNOC) and dinitrobutylphenol (DNBP). Med Lanbovwhoge School Opzoekingstaa Staa Gent, 29: 1189–1197 as cited in US EPA Health advisory for dinoseb (draft), Office of Drinking Water (1987).

Table X20-3: Selected Occupational endpoints: Thresholds and dose response[689]				
Effects	Threshold		Dose response curve	
	Converted (mg/m^3)	Range of Slope Applicability	Converted (mg/m^3)	Slope ($\%/mg/m^3$)
Increased litters with external, internal and skeletal defects (primarily brain and spinal cord)	8.75	8.75	20.4	3.4
Decrease in epididymal sperm count	27.3	27.3	11.6	-2.60
Decreased fertility index for 0-14 days post-treatment mating period	15.9	15.9	11.4	-7.9
Decreased fertility index for 104-112 days post-treatment mating period	15.9	15.9	11.4	-7.0
Decrease in % of embryo survival rate per litter at Day 12	16.2	16.2	2.85	-8.8
Decrease in percentage of foetal survival rate per litter at birth	12.1	12.1	4.08	-4.4
Decreased litters with live foetuses	8.75	8.75	17.5	-4.2
Foetuses with microphthalmia	2.63	2.63	23.6	0.39
Decrease in foetal crown-rump length	14.0	14	1.75	-7.3
Decrease in foetal weight	11.0	11	2.98	-2.7
Reduced foetal birth weight per litter	16.2	16.2	2.85	-2.2
Reduced body weight on postpartum day 1	14.0	14	1.75	-6.8
Reduced body weight on postpartum day 7	14.0	14	1.75	-6.6

X20.3 Relevant sectors, uses and operations

Dinoseb is a phenolic herbicide that is used on soybeans, vegetables, fruits and nuts, citrus, and other field crops for the selective control of grass and broadleaf weeds. The substance has also previously been used as an insecticide on grapes and has also been used as a seed crop drying agent. [690] The substance was banned for use as a pesticide in the EU in 1991. Dinoseb and its salts and esters, under Annex III of the Stockholm Convention is severely restricted or banned for use as a pesticide.

Dinoseb is currently used as a process regulator for polymerisation processes and is used for this purpose in the manufacture of bulk, large scale chemicals (including petroleum products) and in the manufacture of plastics products, including compounding and conversion. The total tonnage manufactured/imported for this use is >=10 tonnes per year per registrant.[691] In Canada; 100,000-1,000,000 tonnes of dinoseb were imported into Canada in 2015 for use as a polymerisation retarder

[689] Threshold: the lowest concentration at which an effect was observed; Slope applicability: The range above the threshold where one might reasonably expect a linear relationship to exist; and Dose Response curve: the slope of the dose response curve in the applicability range above the threshold.

[690] EXTOXNET (undated): Dinoseb. Available at: http://extoxnet.orst.edu/pips/dinoseb.htm

[691] ECHA (2018): Dinoseb- Uses at Industrial Sites. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/12446/3/1/4

in the production of styrene monomer.[692] The process has been described by a company in their submission for the identification of dinoseb as a SVHC.[693] For this process, dinoseb is generally used as a concentrated solution in ethylbenzene in drums or containers and then either transferred to storage tanks or directly into the process. In styrene manufacturing, dinoseb then leaves the production process after distillation with tar steam (typically contains 1-9% of dinoseb) and this is then either for industrial power generation or disposed via incineration. There is also the chance that dinoseb may also be present in further products due to its high vapour pressure. The company also in its submission, states that alternatives to dinoseb are being used in styrene manufacturing. There are two REACH registrants for dinoseb: Addivant and Nufarm. Addivant market a 70% ethylbenzene inhibitor that contains dinoseb.[694] Nufarm market the AHM series of polymerisation inhibitors that contain DNBP (dinoseb).[695]

Imports of Dinoseb exceeded 1,000 tons per year in Organisation for Economic Co-operation and Development (OECD) member countries in 2004.[696] Under PIC notifications, the United Kingdom is the only listed exporting country in the EU. Destinations include: Brazil, Canada, China, Iran, Japan, Malaysia, Taiwan and United States with dinoseb, mixtures of dinoseb (60% and 70%) and other mixtures containing dinoseb such as dinoseb in ethylbenzene.[697] From explicit consents under PIC, dinoseb has been exported from the United Kingdom for use as an industrial chemical with applications involving pesticides listed as pending as of 24th July 2018.

Dinoseb, under its REACH registration dossier is registered for use in closed systems and for transfer in manufacture and its use at industrial sites as a process regulator. Dinoseb is also considered to be used in a closed system for use as a polymerisation inhibitor.[698]

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[692] Government of Canada (2018): Draft screen assessment for dinoseb. Available at: https://www.canada.ca/en/environment-climate-change/services/evaluating-existing-substances/screening-assessment-dinoseb.html

[693] ECHA (2011): Comments on an Annex XV dossier for Identification of a Substance as SVHC and Responses to these comments- Dinoseb. Dated 19 November 2011. Available at: https://echa.europa.eu/documents/10162/791ab610-ceeb-4caf-b355-aad194a809ac

[694] Addivant (2018): Naugard® I-5 30% EB Inhibitor. Available at: https://www.addivant.com/content/naugard%C2%AE-i-5-30-eb-inhibitor

[695] Nufarm (2018): Polymerisation Inhibitors. Available at: http://www.nufarm.com/UK/PolymerisationInhibitors

[696] OECD. (2004). The 2004 OECD List of High Production Volume Chemicals. Available at: http://www.oecd.org/dataoecd/55/38/33883530.pdf.

[697] ECHA (2018): PIC Export Notifications dinoseb. Available at: https://echa.europa.eu/information-on-chemicals/pic/export-notifications?p_p_id=exportnotifications_WAR_echapicportlet&p_p_lifecycle=0&p_p_state=normal&p_p_mode=view&p_p_col_id=column-1&p_p_col_pos=2&p_p_col_count=3&_exportnotifications_WAR_echapicportlet_advancedSearch=false&_exportnotifications_WAR_echapicportlet_keywords=&_exportnotifications_WAR_echapicportlet_highlightedname=dinoseb&_exportnotifications_WAR_echapicportlet_highlightedecnumber=201-861-7&_exportnotifications_WAR_echapicportlet_highlightedcasnumber=88-85-7&_exportnotifications_WAR_echapicportlet_highlightedsearch=true&_exportnotifications_WAR_echapicportlet_orderByType=desc&_exportnotifications_WAR_echapicportlet_orderByCol=orderByYear&_exportnotifications_WAR_echapicportlet_andOperator=true&_exportnotifications_WAR_echapicportlet_searchOrderByCol=&_exportnotifications_WAR_echapicportlet_searchOrderByType=&_exportnotifications_WAR_echapicportlet_resetCur=false&_exportnotifications_WAR_echapicportlet_delta=200

[698] OECD (2007): SIDS Initial Assessment Report for SIAM 24 2-sec-butyl-4,6-dinitrophenol. Available at: https://hpvchemicals.oecd.org/UI/SIDS_Details.aspx?key=56bf41ee-7dba-4bcc-9b8c-16beaf177932&idx=0

Table X20-4: Registered processes of dinoseb in manufacturing and at industrial sites	
PROC Code	**Description**
PROC 1	Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions
PROC 2	Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions
PROC 3	Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions
PROC 8b	Transfer of substance or mixture (charging and discharging) at dedicated facilities
Source: ECHA (2018): Dinoseb REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/12446/1	

A summary of the sectors and uses where dinoseb is used is presented in the following table.

Table X20-5: Dinoseb sectors and uses		
Sector	**Uses and/or activities**	**Notes**
Manufacture of chemicals	Manufacture of dinoseb as an industrial chemical; used in the manufacture of bulk, large scale chemicals	C20 Manufacture of chemicals and chemical products
Manufacture of pesticides and other agrochemical products	Historically used as a pesticide	C20.2 Manufacture of pesticides and other agrochemical products
Plastics	Dinoseb is used as a process regulator for polymerisation (styrene)	C22.2 Manufacture of plastic products

X20.4 Exposed workforce

X20.4.1 Total number of exposed workers

Estimates identified through literature review and consultation for this study

Through literature review, there is no publically available information on the number of exposed workers. The exposed workforce, can however, be estimated, for the purposes of this study, based on employment figures indirectly related to dinoseb, and a number of assumptions based on available data. For dinoseb, as the only effect above the threshold (100x DNEL) is foetuses with microphthalmia (developmental effect), only female workers of reproductive age are considered.

The evidence is outlined below and the assumptions, based on this are summarised in Table X20-6

Manufacture of chemicals

Dinoseb has limited uses, although is registered in the 1000- 10000 tonnes per annum tonnage band. The substance is exported to non-EU countries (such as Canada and China) for use in the manufacture of plastic products, with only the United Kingdom listed as an exporting country. There are also only two registrants in the REACH dossier suggesting that the substance is not manufactured at many sites in the EU.

Manufacture of pesticides and other agrochemical products

This use has not been considered for calculating the number of exposed workers as the use of dinoseb as a pesticide is banned in the EU.

Manufacture of plastic products

Dinoseb is used as a process regulator/polymerisation inhibitor in the manufacture of styrene with the use of closed systems. There are alternatives to the use of dinoseb (DNBP) and these have been applied to styrene plants in Europe.[699] The substance is exported to non-EU countries (such as Canada and China) for use in the manufacture of plastic products, with only the United Kingdom listed as an exporting country.

Table X20-6: Exposed workforce by sector

Sector	Assumptions	Number of exposed workers of reproductive age
Manufacture of basic chemicals, fertilisers and nitrogen compounds, plastics and synthetic rubber in primary forms (C20.1)	• 1,243,800 workers of reproductive age in C20 • 30% of C20 enterprises are C20.1; • 1% of chemical manufacturing plants are manufacturing dinoseb; • 10-20% of workers manufacturing dinoseb are exposed to dinoseb	373-746 workers
Manufacture of plastic products (C22.2)	• 1,617,000 workers of reproductive age in C22; • 88% of C22 enterprises are manufacture of plastic products (C22.2); • 1% are using dinoseb in the manufacturing of plastic products; • 10%-20% of these workers are exposed to dinoseb	1258-2517 workers
Source: Eurostat		

Due to the lack of information on the number of exposed workers to dinoseb from consultation and literature review, a number of assumptions have been used in the above table:

- Eurostat has been used for the number of workers of reproductive age and enterprises;
- For the manufacturing of dinoseb, it has been assumed that 1% of chemical manufacturing plants are manufacturing dinoseb. This assumption has been based on its REACH registration tonnage band (1 000 - 10 000 tonnes per year) and the limited number of REACH registrants (two registrants). This is also likely to be an overestimate;
- 10-20% of workers manufacturing dinoseb have been assumed to be exposed. This assumption has been based on the PROC codes listed in the REACH registration dossier for

[699] ECHA (2011): Comments on an Annex XV dossier for Identification of a Substance as SVHC and Responses to these comments- Dinoseb. Dated 19 November 2011. Available at: https://echa.europa.eu/documents/10162/791ab610-ceeb-4caf-b355-aad194a809ac

manufacturing (PROC 1-3 and 8b). From these PROC codes, some exposure may be possible (for example sampling and testing);

- For the manufacturing of dinoseb in the manufacturing of plastic products, 1% of companies are presumed to be using the substance. This assumption has been based on its REACH registration tonnage band (1 000 - 10 000 tonnes per year) and also that "*the substitution of DNBP is possible as alternative substances have already been successfully applied to European styrene plants*".[700] There is also limited information available on its use in plastic products; and

- 10-20% of workers have been assumed to be potentially exposed in the manufacturing of plastic products. This assumption has been based that exposure may occur in PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions and PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities in its REACH registration dossier. The process used is described in section X20.3.

Breakdown by gender and age

Table X20-7: Exposed workforce by gender and age		
Sector	**Assumptions**	**Number of exposed workers of reproductive age**
Manufacture of basic chemicals, fertilisers and nitrogen compounds, plastics and synthetic rubber in primary forms (C20.1)	• 1,243,800 workers of reproductive age in C20 • 30% of C20 enterprises are C20.1; • 1% of chemical manufacturing plants are manufacturing dinoseb; • 10-20% of workers manufacturing dinoseb are exposed to dinoseb	Male: 281-562 workers Female: 92-184 workers
Manufacture of plastic products (C22.2)	• 1,617,000 workers of reproductive age in C22; • 88% of C22 enterprises are manufacture of plastic products (C22.2); • 1% are using dinoseb in the manufacturing of plastic products; • 10%-20% of these workers are exposed to dinoseb	Male: 1093-2187 workers Female: 165-330 workers
Source: Eurostat		

Trends

Exposure to dinoseb has decreased over the years. Dinoseb was previously used for agricultural uses (herbicide and insecticide) however this use has been banned in the EU; so before this ban the number of workers exposed would have been much greater. Exposure to dinoseb may also decrease in the future with alternatives being used in styrene manufacture.

[700] ECHA (2011): Comments on an Annex XV dossier for Identification of a Substance as SVHC and Responses to these comments- Dinoseb. Dated 19 November 2011. Available at: https://echa.europa.eu/documents/10162/791ab610-ceeb-4caf-b355-aad194a809ac

Exposed workers: conclusion

The total number of potentially exposed workers is summarised below.

Table X20-8: Exposed workforce: conclusion			
Estimate	**No of exposed workers**	**Men of reproductive age**	**Women of reproductive age**
High estimate	3263	2749	514
Low estimate	1631	1374	257
Alternative estimate for the sensitivity analysis	-	-	-
Annual rate of change taken forward for modelling	4%	4%	4%

X20.5 Exposure levels

X20.5.1 Exposure routes

Occupational exposure to dinoseb can occur from spraying and mixing operations from manufacture and its applications. Exposure could also occur during the transfer of the substance or mixture (charging and discharging) at dedicated facilities. Exposure routes of dinoseb are from dermal contact and inhalation of aerosols.[701]

The dominant route of exposure is dermal exposure and the substance is rapidly absorbed through the skin.

X20.5.2 Current exposure levels

There is no publicly available information on current occupational exposure levels. From confidential sources, the reported exposure levels are <0.2 mg/m^3. Previously, occupational exposure to dinoseb could occur as a result of spraying and mixing operations during its manufacture and application. Estimates of worker (applicators, mixers, loaders, etc.) exposure based on field measurements showed a NOEL of 3 mg/kg bw/day.[702]

Dinoseb, from its REACH registration is used in closed processes where occupational exposure may occur with equivalent containment conditions (exposure would be assumed to be low) and exposure could also occur from the transfer of the substance at dedicated facilities (charging and discharging).

X20.5.3 Trends

There is no available information on exposure trends for occupational exposure to dinoseb.

[701] OECD (2007): SIDS Initial Assessment Report for SIAM 24 2-sec-butyl-4,6-dinitrophenol. Available at: https://hpvchemicals.oecd.org/UI/SIDS_Details.aspx?key=56bf41ee-7dba-4bcc-9b8c-16beaf177932&idx=0

[702] Food and Agriculture Organisation of the United Nations (1991): Dinoseb and its salts and esters: Decision Guidance documents. Available at: http://www.pic.int/Portals/5/DGDs/DGD_Dinoseb%20and%20salts%20and%20esters_EN.pdf

X20.6 Current Risk Management Measures (RMMs)

X20.6.1 Overview of RMMs

As discussed in section X20.4, occupational exposure to dinoseb can occur *via* dermal and inhalation exposure routes. Recommended risk management measures in place for dermal exposure are the use of gloves and protective clothing and for inhalation, sufficient ventilation is recommended. Closed processes are a risk management measure that is employed for the following PROC codes:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions; and
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions

Risk management measures that are recommended for reducing exposure (apart from the use of closed systems) which are listed in the REACH registration dossier are discussed in the following table. PROC codes with exposure include:

- PROC 4: Chemical production where opportunity for exposure arises; and
- PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities.

Table X20-9: Dinoseb REACH protective measures	
Measure	**Details**
Organisational measures	Do not eat or drink at work; immediately remove contaminated clothing
Engineering measures	Ensure there is sufficient ventilation; storage room floor must be impermeable to prevent the escape of liquids
Respiratory protection	For emergencies: use self-contained breathing apparatus; Particle filter size P1 (EN143)
Eye protection	Safety glasses with side shields
Hand protection	Compatible chemical resistant gloves
Skin and body protection	Protective clothing
Source: ECHA (2018): Dinoseb REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/12446/9	

X20.6.2 Best/good practice examples

An example of best/good example is for the use of dinoseb in the manufacture of plastic products which was received during the consultation process for the Annex XV dossier from one company in Germany.[703] The substitution of the substance is possible and has been undertaken at styrene plants in Europe. One alternative substance (details of this substance have not been provided) has properties that compared to DNBP are advantageous such as lower acute toxicity for dermal and inhalation exposure, no potential eye and skin irritation and no sensitisation potential.

[703] ECHA (2011): Comments on an Annex XV dossier for Identification of a Substance as SVHC and Responses to these comments- Dinoseb. Dated 19 November 2011. Available at: https://echa.europa.eu/documents/10162/791ab610-ceeb-4caf-b355-aad194a809ac

X20.6.3 Voluntary industry initiatives

No voluntary industry initiatives have been identified for dinoseb.

X20.7 Market analysis

The socio-economic characteristics of the sectors in which dinoseb exposure may occur are summarised below.

- C20.1 Manufacture of basic chemicals, fertilisers and nitrogen compounds, plastics and synthetic rubber in primary forms
- C20.2 Manufacture of pesticides and other agrochemical products
- C22.2 Manufacture of plastic products

X20.7.1 Number of SMEs in each sector

Table X20-10: Number and proportion of SMEs by size of enterprise and sector									
Sector	TOTAL	Micro		Small		Medium		Large	
	No. firms	No. firms	% of total	No. firms	% of total	No. firms	% of total	No. firms	% of total
C20.1	**8,980**	5,190	58%	2,010	22%	980	11%	360	4%
C20.2	**630**	360	57%	140	22%	100	16%	20	3%
C22.2	**54,220**	35,490	65%	13,050	24%	4,900	9%	780	1%
Source: Eurostat's Structural Business Statistics database									

X20.7.2 Average turnover by size of enterprise

Table X20-11: Average turnover by sector and size of enterprise, 2016												
Sector	Micro			Small			Medium			Large		
	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m
C20.1	6,854	5,190	1.32	19,422	2,010	9.66	68,909	980	70.32	234,358	360	650.99
C20.2	194	360	0.54	852	140	6.09	4,697	100	46.97	5,005	20	250.25
C22.2	11,410	35,490	0.32	46,395	13,050	3.56	98,462	4,900	20.09	78,698	780	100.89
Source: Eurostat's Structural Business Statistics database												

X20.7.3 R&D expenditure

Table X20-12: Business expenditure on R&D per sector (in € million), EU28		
Sector	Data availability	R&D expenditure (in €m)
C20.1	C20	6,659.7
C20.2	C20	6,659.7
C22.2	C22	2,371
Source: Eurostat Notes: EU28 totals do not include data for some member states, due to confidentiality.		

X20.8 Burden of ill health

X20.8.1 Cases of ill health

To assess the potential cases of ill health, two exposure scenarios have been considered as there is no exposure data available:

- Member state OEL: 0.1 mg/m^3 (Romania); and
- 100 x DNEL (inhalation): 4 mg/m^3

OEL exposure scenario

The threshold for effect (lowest effect threshold is 2.63 mg/m^3) does not lie below the OEL set by Romania of 0.1 mg/m^3 for any endpoint measure. If it is assumed that no workers are exposed to dinoseb above this OEL, then no fertility or developmental effects will occur in those working with dinoseb.

100x DNEL scenario

One endpoint has a threshold for effect that lies above 4 mg/m^3 dinoseb (100 x DNEL). This is foetuses with microphthalmia.

For the number of cases, the number of potentially exposed workers (female) is between 257-514 workers. For these values:

- A value of 2.83% for females giving birth has been used (0.0283 x 257; 0.0283 x 514 = 7-14 babies);
- An incidence rate of 9% (based on the study for this effect) has been used which gives rise to 0.65 and 1.31;[704] and
- A value of 0.5% has been derived from the DRR which gives rate to a number of cases of 0.345-0.69.

Table X20-13: Dinoseb – effects used for estimation

Effect	Threshold	DRR	Value	Cases
Foetuses with microphthalmia	2.63	y=0.39x-1.0257	0.5	0.345-0.69

This effect may also be able to be monetised. In terms of the number of cases, this would likely have been higher in the past when dinoseb was previously used for agricultural uses and so there has been a decrease in exposure over time.

[704] Giavini E et al (1986): Effect of method of administration on the teratogenicity of dinoseb in the rat Arch. Environ. Contam. Toxicol. 15, pp 377-384. As cited in ECHA dossier of Dinoseb. https://echa.europa.eu/hu/registration-dossier/-/registered-dossier/12446/7/9/3/?documentUUID=ab4e6fd9-2929-4853-82e1-8fdb5af0b85e

Annex 21 Aprotic Solvents

X21.1 Introduction to aprotic solvents

X21.1.1 Relevant solvents

Aprotic solvents (also known as aprotic polar solvents) are solvents that may contain hydrogens but do not contain O-H (hydroxyl) or N-H bonds in their structure (lack protons) and cannot hydrogen bond. Aprotic solvents allow the reaction of ionic compounds as they solvate cations.[705]

X21.1.2 Hazard classification(s)

Aprotic solvents that are classified as being reproductive toxins only (Repr. 1B) are 1-methyl-2-pyrrolidone (NMP), N,N-dimethylformamide (DMF) and N,N-dimethylacetamide (DMAC).[706] Dimethyl sulfoxide (DMSO) is an aprotic solvent with use in EU; however this solvent is not classified as a reprotoxin.[707]

Table X21-1: Relevant R 1A/1B aprotic solvents

Solvent	CAS no	EC no	Classification
N,N-dimethylacetamide (DMAC)	127-19-5	204-826-4	Repr. 1B H360D May damage the unborn child
N,N-dimethylformamide (DMF)	68-12-2	200-679-5	Repr. 1B H360D May damage the unborn child
1-methyl-2-pyrrolidone (NMP)	872-50-4	212-828-1	Repr. 1B H360D May damage the unborn child

X21.1.3 Existing OELs and BLVs

Indicative OEL under Chemicals Agent Directive (CAD)

DMAC, DMF and NMP all have indicative OELVs under CAD. The 8-hr TWA OELVs are as follows:

- DMAC: 10 ppm (36 mg/m^3) with a skin notation.
- DMF: 5 ppm (15 mg/m^3) with a skin notation; and
- NMP: 10 ppm (40 mg/m^3) with a skin notation.

The indicative short term OELVs are:

- DMAC: 20 ppm (72 mg/m^3)
- DMF: 10 ppm (30 mg/m^3); and

[705] Oxford University Press (2007): The Effect on Solvent on Nucleophilicity. Available at: http://staff.du.edu.eg/upfilestaff/447/courses/8447_1458459204__Nucleophilic2._.pdf

[706] Bergkamp L and Herbatschek N (2014): Regulating Chemical Substances under REACH: The Choice between Authorisation and Restriction and the Case of Dipolar Aprotic Solvents. RECIEL, 23(2), pp 221-245.

[707] ECHA (2018): Dimethyl sulfoxide Substance Information. Available at: https://echa.europa.eu/substance-information/-/substanceinfo/100.000.604

- NMP: 20 ppm (80 mg/m^3).

Member State OELs

N,N-dimethylacetamide (DMAC)

For member states with national OELs for DMAC, the majority of member states have the same 8-hr TWA OEL as the indicative CAD OEL of 10 ppm (36 mg/m^3). France has a lower OEL and there are no OELs above the CAD indicative OEL.

Table X21-2: National OELs for DMAC		
Country	**8 hr TWA OEL**	**Short term OEL**
Belgium	10 ppm; 36 mg/m^3	20 ppm; 72 mg/m^3
Denmark	10 ppm; 36 mg/m^3	20 ppm; 72 mg/m^3
Finland	10 ppm; 36 mg/m^3	20 ppm; 72 mg/m^3
France	2 ppm; 7.2 mg/m^3	10 ppm; 36 mg/m^3
Germany	10 ppm; 36 mg/m^3	20 ppm; 72 mg/m^3
Hungary	10 ppm; 36 mg/m^3	20 ppm; 72 mg/m^3
Ireland	10 ppm; 36 mg/m^3	20 ppm; 72 mg/m^3
Italy	10 ppm; 36 mg/m^3	20 ppm; 72 mg/m^3
Latvia	10 ppm; 36 mg/m^3	20 ppm; 72 mg/m^3
Portugal	10 ppm; 36 mg/m^3	20 ppm; 72 mg/m^3
Spain	10 ppm; 36 mg/m^3	20 ppm; 72 mg/m^3
Sweden	10 ppm; 35 mg/m^3	20 ppm; 70 mg/m^3
The Netherlands	10 ppm; 36 mg/m^3	20 ppm; 72 mg/m^3
United Kingdom	10 ppm; 36 mg/m^3	20 ppm; 72 mg/m^3
Sources: ECHA (2018): Analysis of the most appropriate regulatory management option: N,N-Dimethylacetamide; Dimethylformamide (DMF); N-methyl pyrrolidone (NMP). Available at: https://echa.europa.eu/documents/10162/f96ae430-bfba-f349-36aa-fd9cc13c4f01		

N,N-Dimethylformamide (DMF)

OELs and STEL for DMF for member states are presented in the following table. Eleven member states have the same OEL as the indicative OEL under CAD of 5 ppm (15 mg/m^3). The highest OEL is 10 ppm (30 mg/m^3).

Table X21-3: National OELs for DMF		
Country	**8 hr TWA OEL**	**Short term OEL**
Austria	5 ppm; 15 mg/m^3	10 ppm; 30 mg/m^3
Belgium	10 ppm; 30 mg/m^3	-
Denmark	10 ppm; 30 mg/m^3	20 ppm; 60 mg/m^3
Finland	5 ppm; 15 mg/m^3	10 ppm ;30 mg/m^3
France	5 ppm; 15 mg/m^3	10 ppm ;30 mg/m^3
Germany	5 ppm; 15 mg/m^3	10 ppm ;30 mg/m^3
Hungary	10 ppm; 30 mg/m^3	40 ppm; 120 mg/m^3
Ireland	5 ppm; 15 mg/m^3	10 ppm ;30 mg/m^3
Italy	5 ppm; 15 mg/m^3	10 ppm ;30 mg/m^3
Latvia	10 ppm; 30 mg/m^3	15 ppm; 45 mg/m^3
Poland	5 ppm; 15 mg/m^3	10 ppm; 30 mg/m^3
Portugal	5 ppm; 15 mg/m^3	10 ppm ;30 mg/m^3
Spain	5 ppm; 15 mg/m^3	10 ppm ;30 mg/m^3

Table X21-3: National OELs for DMF		
Country	**8 hr TWA OEL**	**Short term OEL**
Sweden	5 ppm; 15 mg/m^3	10 ppm ;30 mg/m^3
The Netherlands	5 ppm; 15 mg/m^3	10 ppm ;30 mg/m^3
United Kingdom	10 ppm; 30 mg/m^3	20 ppm; 60 mg/m^3
Sources: ECHA (2018): Analysis of the most appropriate regulatory management option: N,N-Dimethylacetamide; Dimethylformamide (DMF); N-methyl pyrrolidone (NMP). Available at: https://echa.europa.eu/documents/10162/f96ae430-bfba-f349-36aa-fd9cc13c4f01		

1-methyl-2-pyrrolidone (NMP)

For member states with national OELs for NMP, 11 member states have the same 8-hr TWA OEL as the indicative CAD OEL of 10 ppm (40 mg/m^3). Denmark has lower OEL of 5 ppm (20 mg/m^3); whilst Latvia, and Spain have higher OELs (25 ppm).

Table X21-4: National OELs for NMP		
Country	**8 hr TWA OEL**	**Short term OEL**
Austria	10 ppm; 40 mg/m^3	20 ppm; 80 mg/m^3
Belgium	10 ppm; 40 mg/m^3	20 ppm; 80 mg/m^3
Denmark	5 ppm; 20 mg/m^3	10 ppm; 40 mg/m^3
Finland	10 ppm; 40 mg/m^3	20 ppm; 80 mg/m^3
France	10 ppm; 40 mg/m^3	20 ppm; 80 mg/m^3
Germany	20 ppm; 82 mg/m^3	40 ppm; 164 mg/m^3
Ireland	10 ppm; 40 mg/m^3	20 ppm; 80 mg/m^3
Italy	10 ppm; 40 mg/m^3	20 ppm; 80 mg/m^3
Latvia	25 ppm; 103 mg/m^3	-
Poland	10 ppm; 40 mg/m^3	20 ppm; 80 mg/m^3
Portugal	10 ppm; 40 mg/m^3	20 ppm; 80 mg/m^3
Spain	10 ppm; 40 mg/m^3	20 ppm; 80 mg/m^3
Sweden	10 ppm; 40 mg/m^3	20 ppm; 80 mg/m^3
The Netherlands	10 ppm; 40 mg/m^3	20 ppm; 80 mg/m^3
United Kingdom	10 mg/m^3; 40 ppm	20 mg/m^3; 80 ppm
Sources: ECHA (2018): Analysis of the most appropriate regulatory management option: N,N-Dimethylacetamide; Dimethylformamide (DMF); N-methyl pyrrolidone (NMP). Available at: https://echa.europa.eu/documents/10162/f96ae430-bfba-f349-36aa-fd9cc13c4f01		

DNEL (Derived No Effect Level)

The Derived No Effect Levels for NMP, DMF and DMAC from their respective REACH registration dossiers are discussed in the following table.

Table X21-5: DNELs for NMP, DMF and DMAC	
Substance	**DNEL**
N,N-dimethylacetamide (DMAC)	**Inhalation:** Long term, systemic: 23 mg/m^3 Short term, acute: 120 mg/m^3 **Dermal:** Long term, systemic: 11 mg/kg bw/day Short term, acute: 42 mg/kg bw/day
N,N-dimethylformamide (DMF)	**Inhalation:** Long term, systemic: 15 mg/m^3 Short term, acute: 30 mg/m^3 Long term, local: 15 mg/m^3 **Dermal:** Long term, systemic: 3.31 mg/kg bw/day Short term, systemic: 26.3 mg/kg bw/day Long term, local: 446 µg/cm^2 Short term: 5 900 µg/cm^2
1-methyl-2-pyrrolidone (NMP)	Long term exposure, inhalation, systemic: 14.4 mg/m^3 Local effects, long term exposure: 40 mg/m^3

X21.1.4 Legislation other than CAD

REACH measures

Restriction

NMP will be restricted under REACH from 2020. The conditions of this restriction are that:[708]

- *"The substance shall not be placed in the market as a substance on its own or in mixtures in a concentration equal to or greater than 0,3 % after 9 May 2020 unless manufacturers, importers and downstream users have included in the relevant chemical safety reports and safety data sheets, Derived No-Effect Levels (DNELs) relating to exposure of workers of 14,4 mg/m^3 for exposure by inhalation and 4,8 mg/kg/day for dermal exposure";*
- *"Shall not be manufactured, or used, as a substance on its own or in mixtures in a concentration equal to or greater than 0,3 % after 9 May 2020 unless manufacturers and downstream users take the appropriate risk management measures and provide the appropriate operational conditions to ensure that exposure of workers is below the DNELs specified in paragraph 1"; and*
- *By way of derogation from paragraphs 1 and 2, the obligations laid down therein shall apply from 9 May 2024 in relation to placing on the market for use, or use, as a solvent or reactant in the process of coating wires"*

[708] ECHA (undated): Annex XVII to REACH- Conditions of restriction. Available at: https://echa.europa.eu/documents/10162/e7598958-eae7-1661-0636-02778b427efc

Italy has also submitted a proposal for a restriction for DMF to restrict the use of DMF on its own or as part of a mixture for concentrations either equal to or greater than 0.3%. This proposal is that manufacturers, imported and downstream users who use the substance either on its own or in mixtures equal or greater than 0.3% shall use a DNEL value for long term inhalation exposure of 3.2 mg/m^3 and a long term harmonised worker-based DNEL value of 0.79 mg/kg bw/day in their chemical safety assessment and safety data sheets.[709]

Candidate list

NMP, DMF and DMAC are all on the candidate list for authorisation as being toxic for reproduction (Article 57(c)).

Other legislation

NMP, DMF and DMAC are restricted under the Toy Safety Directive. NMP, DMF and DMAC are also subject to directives 2001/83/EC on medicinal products for human use and 2001/82/EC on veterinary medicinal products for the production of medicinal products. They are also subject to Commission Delegated Regulation (EU) No 1252/2014 for good manufacturing practice for medicinal products for human uses.

NMP is also listed in table 1 of Annex I (entry 376) for Regulation (EC) No 10/2011 for plastic materials. Its use is only authorised when used as a polymer production aid or additive.

X21.2 Summary of health endpoints, thresholds & DRRs

X21.2.1 Relevant health endpoints

N,N-dimethylacetamide (DMAC)

The reproductive effects, which have been deemed as potentially relevant to humans identified through literature review are summarised in the following table.

Table X21-6: DMAC– summary of reproductive health effects

Health effects	Fertility/ development		Male/ Female exposure	Monetisable effect correlate
	Fer	Dev		
Parturition Index[710]	Fer		F	
Miscellaneous effects[710]	Fer	Dev	F	No quantitative data available
Reduced Body Weight at 21 days[711]		Dev	F	Reduced foetal growth

[709] ECHA (2018): Annex XV Restriction Report. Proposal for a Restriction. Dimethylformamide (DMF). Available at: https://echa.europa.eu/documents/10162/9aa67e9e-0adb-7eda-53f9-021b700889d9

[710] ECHA (2018): Unnamed study report as cited in WOE 001 of N,N-dimethylacetamide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15266/7/9/

[711] ECHA (2018): Ferenz RL and Kennedy GL (1986): Reproduction study of dimethylacetamide following inhalation in the rat. Fundam Appl Toxicol 7: 132-137 as cited in WOE 002 of N, N-dimethylacetamide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15266/7/9/2/?documentUUID=2457f531-6d39-41a0-aeb5-17e868a7a2b8

Table X21-6: DMAC– summary of reproductive health effects				
Significant foetotoxicity (reduced body weight)[712]		Dev	F	Low birth weight, Reduced foetal growth
Reduced # of live male foetuses / litter[713]	Fer	Dev	F	Spontaneous abortion or still birth
Reduced foetal weight male[713]		Dev	F	Low birth weight
Reduced foetal weight females		Dev	F	Low birth weight
Early resorption/litter[714]	Fer		F	Spontaneous abortion or still birth
Reduced # of live foetuses per litter[714]	Fer		F	Spontaneous abortion or still birth
Reduced mean foetal weight[714]		Dev	F	Low birth weight
Foetal malformations[715]		Dev	M/F	No monetisable effect correlate
Foetal weight [715]		Dev	M/F	Low birth weight
Number of dead implants [715]	Fer		M/F	Spontaneous abortion or still birth
No teratogenic effects observed[716]		Dev	F	-
% resorptions per dam[717]	Fer		F	Spontaneous abortion or still birth
Foetal Weight [717]		Dev	F	Low birth weight, reduced foetal growth
Foetal weight (inhalation)[718]		Dev	F	Low birth weight
Soft tissue variations (% Foetuses) [718]		Dev	F	No monetisable effect correlate
Skeletal variations (% Foetuses) [718]		Dev	F	Skeletal effects or abnormalities of the limbs

[712] ECHA (2018): Unnamed study report, 1983 as citied in WOE 001 of N,N-dimethylacetamide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15266/7/9/3

[713] ECHA (2018): Okuda H et al, 2006. Developmental toxicity induced by inhalation exposure of pregnant rats to N, N-dimethylacetamide. J Occup Health 48: 154-160 as cited in WOE 002 of N, N-dimethylacetamide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15266/7/9/3/?documentUUID=b4b554b1-49af-4bc7-a0fa-581176bad4b5

[714] ECHA (2018): Unnamed study 1997 cited in WOE 003 of N,N-dimethylacetamide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15266/7/9/3/?documentUUID=b4b554b1-49af-4bc7-a0fa-581176bad4b5

[715] ECHA (2018): Unnamed studies 1975 and 1976 as cited in WOE 004 of N,N-dimethylacetamide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15266/7/9/3/?documentUUID=5721b079-d67e-4b35-ab7e-5b48c0c7f711

[716] ECHA (2018): Solomon HM, 1991. Developmental toxicity of dimethylacetamide by inhalation in the rat. Fund Appl Toxicol 16: 414-422 as cited in WOE 005 of N,N-dimethylacetamide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15266/7/9/3/?documentUUID=0eda03a8-7b1d-40ab-9fad-dc82bfb696c5

[717] ECHA (2018): Unnamed report 1976 and. Merkle, J. et l 1980. Studies on acetamides and formamides for embryotoxic and teratogenic activities in the rabbit. Drug Res 30: 1557-1562 as cited in WOE 006 Dev of N,N-dimethylacetamide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15266/7/9/3/?documentUUID=5860b930-dc35-4508-95a9-6f19f4c8476d

[718] ECHA (2018): Unnamed studies 1989 and Klimisch HJ et al, 2000. Developmental toxicity of dimethylacetamide in rabbits following inhalation exposure. Human Exp Toxicol 19: 676-683 as cited in WOE 007 of N,N-dimethylacetamide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15266/7/9/3/?documentUUID=2dba6f2b-5fdd-4e38-aa0d-6a60927cfbe8

Table X21-6: DMAC– summary of reproductive health effects				
Teratogenic effect[719]		Dev	F	No quantitative data
% dead implants[720]	Fer	Dev	F	Spontaneous abortion or still birth
Foetal weight [720]		Dev	F	Low birth weight
% foetuses with malformations [720]		Dev	F	No monetisable effect correlate
No Effects[721]			F	Very small exposure regimen
% malformations[722]		Dev	F	No monetisable effect correlate
Viable foetuses (per litter)[723]	Fer	Dev	F	Spontaneous abortion or still birth
Resorption sites per litter [723]	Fer	Dev	F	Spontaneous abortion or still birth
Mean foetal body weight[724]		Dev	F	Low birth weight
24 h viability index [724]		Dev	F	Spontaneous abortion or still birth

N,N-dimethylformamide (DMF)

The reproductive effects, which have been deemed as potentially relevant to humans identified through literature review are summarised in the following table.

Table X21-7: DMF– summary of reproductive health effects				
Health effects	**Fertility/ development**		**Male/ Female exposure**	**Monetisable effect correlate**
	Fer	**Dev**		
Fertility/fecundity[725]	Fer		F	Impaired or reduced fertility-female
Abnormal appearance[725] (Visible deformities- external malformations)		Dev	F	No monetisable effect correlate

[719] ECHA (2018): Johannsen, FR et al, 1987. Teratogenic response of dimethylacetamide in rats. Fund Appl Tox 9: 550-556 as citied in WOE 008 of N,N-dimethylacetamide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15266/7/9/3/?documentUUID=f3cf2bad-c12a-443d-9577-aff228990930

[720] ECHA (2018): Unnamed study reports 1975 and 1976 as cited in WOE 009 of N,N-dimethylacetamide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15266/7/9/3/?documentUUID=03288b6e-e7aa-4725-91da-4372823330cc

[721] ECHA (2018): Unnamed study report 1973 as cited in WOE 10 of N,N-dimethylacetamide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15266/7/9/3/?documentUUID=2a9cda50-18da-48d0-bf5a-a7624c223817

[722] ECHA (2018): Unnamed study report 1974 as cited in WOE 011 of N,N-dimethylacetamide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15266/7/9/3/?documentUUID=a674fa97-da2d-491e-a340-cf2c8d80b7c0

[723] ECHA (2018): Unnamed study report 1972 as cited in WOE 013 of N,N-dimethylacetamide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15266/7/9/3/?documentUUID=a42a159c-119b-48d8-a81c-392836200da4

[724] ECHA (2018): Unnamed study report 1973 as cited in Repro Key 001 of N,N-dimethylacetamide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15266/7/9/3/?documentUUID=228688a6-9bec-4ed5-aeed-c5be2ac359db

[725] ECHA (2018): Unnamed study, 1998 as cited in Repro 001 of N,N-dimethylformamide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15093/7/9/2

Table X21-7: DMF– summary of reproductive health effects				
Skeletal Malformations[725]		Dev	F	Skeletal effects or abnormalities of the limbs
Proportion of litters ext malformed pups[725]		Dev	M/F	No monetisable effect correlate
Skeletal Abnormalities[726]		Dev	F	Skeletal effects or abnormalities of the limbs
Mean foetal body weight[725]		Dev	F	Reduced foetal growth
Total Malformations[725]		Dev	F	Cardiovascular effects-malformations
Total Variations[725]		Dev	F	No monetisable effect correlate

1-methyl-2-pyrrolidone (NMP)

The reproductive effects, which have been deemed as potentially relevant to humans identified through literature review are summarised in the following table.

Table X21-8: NMP – summary of reproductive health effects				
Health effects	**Fertility/ development**		**Male/ Female exposure**	**Monetisable effect correlate**
	Fer	**Dev**		
Viability Index[727]	Fer		F	Spontaneous abortion or still birth
Lactation Index[727]	Fer		F	-
Pup Body weight gain[727]		Dev	F/M	Low birth weight
Live birth index[727]	Fer		F	Spontaneous abortion or still birth
Litters liveborn; dead at day 4		Dev	F/M	Spontaneous abortion or still birth
Viability Index[728]	Fer		F/M	Spontaneous abortion or still birth
Offspring weight per litter[729]	Fer		F/M	Low birth weight
Reduced pup body weights[730]	Fer		F/M	Low birth weight
Fetal Malformations[730]		Dev	F	Skeletal effects or abnormalities of the limbs

[726] ECHA (2018): Unnamed study, 1984 and Hellwig et al 1991, Studies on the prenatal toxicity of N,N-dimethylformamide in mice, rats and rabbits, Fd. Chem. Tox. 29, 193-201 (1991) as cited in N,N-dimethylformamide REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15093/7/9/3

[727] ECHA (2018): Unnamed 1999 study cited in Repro Key 001 of 1-methyl-2-pyrrolidone REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15493/7/9/2

[728] ECHA (2018): Unnamed 1999 study cited in Repro Key 002 of 1-methyl-2-pyrrolidone REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15493/7/9/2/?documentUUID=09f268d2-67aa-416c-a678-2399be799f87

[729] ECHA (2018): Unnamed 1999 study and Solomon et al 1995 Drug Chem. Toxicol., 18(4), 271-293. 1-Methyl-2-pyrrolidone (NMP): reproductive and developmental toxicity study by inhalation in the rat Solomon et al (1997) cited in in WoE 005 of 1-methyl-2-pyrrolidone REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered dossier/15493/7/9/2/?documentUUID=37a5d973-9a1d-45e2-889a-5a267c8f1725

[730] ECHA (2018): Solomon et al 1995 cited in Dev Key 001 of 1-methyl-2-pyrrolidone REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15493/7/9/3

Table X21-8: NMP – summary of reproductive health effects				
Early resorptions[731]	Fer		F	Spontaneous abortion or still birth
External Malformations[731]		Dev	F	Skeletal effects or abnormalities of the limbs
Skeletal Malformations[731]		Dev	F	Skeletal effects or abnormalities of the limbs
Fetal pup Bodyweight females	Fer		F	Low birth weight
Visceral Malformations[731]		Dev	F	liver abnormalities or renal abnormalities
Visceral Variations[731]		Dev		liver abnormalities or renal abnormalities
Skeletal Variations[732]		Dev	F	Skeletal effects or abnormalities of the limbs
Fetal Pup Body weight changes[733]		Dev	F	Low birth weight
Extra 13th Rib[734]		Dev	F	Skeletal effects or abnormalities of the limbs
Resorptions/dam[735]	Fert		F	Spontaneous abortion or still birth
Extra 13th Rib		Dev	F	Skeletal effects or abnormalities of the limbs
Total variations[736]		Dev	F	Skeletal effects or abnormalities of the limbs

[731] ECHA (2018): Unnamed 1991 study cited in Dev Key 002 1-methyl-2-pyrrolidone REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15493/7/9/3/?documentUUID=d03b7ecf-7f73-471a-a70a-c00d4398d105

[732] ECHA (2018): Saillenfait et al 2002 Food and Chem Toxicology 40(11) 1705-1712: Developmental Toxicity of N-Methyl-2- pyrrolidone administered orally to rats as cited in Dev Key 003 of 1-methyl-2-pyrrolidone REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15493/7/9/3/?documentUUID=1dfafce2-74dc-43b7-8a0c-4e3696662551

[733] (a) ECHA (2018): Saillenfait et al 2002 Food and Chem Toxicology 40(11) 1705-1712: Developmental Toxicity of N-Methyl-2- pyrrolidone administered orally to rats as cited in Dev Key 005 of 1-methyl-2-pyrrolidone REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15493/7/9/3/?documentUUID=3f441ac1-a463-4dcc-b72e-1bc3f6362bf5 and (b) Saillenfait et al 2003 Food and Chem Toxicology 41(4) 583-588 Developmental toxicity of N-methyl-2-pyrrolidone in rats following inhalation exposure cited in Dev Key 005 of 1-methyl-2-pyrrolidone REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15493/7/9/3/?documentUUID=3f441ac1-a463-4dcc-b72e-1bc3f6362bf5

[734] ECHA (2018): Unnamed 1993 study as cited in Dev Key 006 of 1-methyl-2-pyrrolidone REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15493/7/9/3/?documentUUID=881102e7-c9bb-40ed-b3bc-2b985d008110

[735] ECHA (2018): Unnamed 1979 study as cited in Dev Key 007 of 1-methyl-2-pyrrolidone REACH registration dossier. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15493/7/9/3/?documentUUID=59cf0206-7cce-40c2-a10e-2626e52923e9

[736] ECHA (2018): Unnamed 1993 study as citied in Dev Key 008. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15493/7/9/3/?documentUUID=b53bc740-797d-42c5-8021-44d95fd96ac4

X21.3 Summary of thresholds and DRRs

The no effect thresholds (inhalation 8-hr TWA mg/m^3) and effect slopes, together with the maximum air exposure concentrations (8-hr TWA mg/m^3) for which the effect slopes are valid, are summarised in the following tables.

N,N-dimethylacetamide (DMAC)

Table X21-9: DMAC Selected Occupational endpoints: Thresholds and dose response					
Effects		Threshold		Dose response curve	
		Converted (mg/m^3)	Range of Applicability for Slope	Converted (mg/m^3)	Slope (%/mg/m^3)
Spontaneous abortion or still birth	Parturition index	875 (625)[737]	1750 (1250)	875 (625)	-0.06
	Live male foetuses/ litter	1730(1648)	2300(2190)	570(543)	-0.07
	Early resorption/ litter	262(250)	525(499)	262(250)	1.98
	Live foetuses/litter	262(250)	525(499)	262(250)	-0.11
	# of dead implants	400	1200	800	0.14
	% resorptions per dam	274(196)	816(583)	542(387)	0.37
	% dead implants	186(133)	188(134)	374(267)	0.27
	Viable foetuses/litter	875	1750	875	-0.07
	Resorption sites/litter	875	875	1750	2.10
Reduced foetal growth	Reduced body weight (21 days)	360	1080	720	-0.02
	Significant foetotoxicity (reduced bw)	384(366)	1080(1029)	696(663)	-0.01
	Foetal weight males	384(366)	1150(1095)	766(730)	-0.01
	Foetal weight females	384(366)	1150(1095)	766(730)	-0.01
	Mean foetal weight	114(109)	262(250)	149(142)	-0.04
	Foetal weight	24	240	216	-0.01
	Foetal weight	274(196)	816(583)	542(387)	-0.03
	Foetal weight	20(19)	200(190)	180(171)	-0.05
	Foetal weight	186(133)	188(134)	374(267)	-0.05
	Mean foetal body weight	729	1458	729	-0.02
	24 H viability index	729	1458	729	-0.02
Skeletal effects or abnormalities of the limbs	Foetal Malformations	400	1200	800	10.61
	Soft tissue variations (% foetuses)	700(667)	2000(1905)	1300(1238)	0.08
	Skeletal variations (% foetuses)	700(667)	2000(1905)	1300(1238)	0.12
	Malformations (% Foetuses)	186	188	374	2.33
	Malformations (%)	274	268	542	2.02
Note: The first number is the data as calculated from the relevant study. The number in brackets is corrected for exposure time (i.e. continuous exposure is converted to 40 hrs a week by multiplying the concentrations by 40/168)					

[737] Values in brackets are corrected for exposure scenario/ duration of exposure

N,N-dimethylformamide (DMF)

Table X21-10: DMF Selected Occupational endpoints: Thresholds and dose response					
Effects		Threshold		Dose response curve	
		Converted (mg/m^3)	Range of Applicability for Slope	Converted (mg/m^3)	Slope ($\%/mg/m^3$)
Impaired/reduced fertility - female	Fertility/fecundity female parent	219 (920)	1455 (6111)	1236 (5191)	-.04 (-0.01)
	Host of other repro effects				NO DATA
Reduced foetal growth	Mean foetal body weight	148 (111)	452 (339)	304 (228)	-0.05(-0.06)
Skeletal effects or abnormalities of the limbs	Skeletal Malformations	219 (920)	820 (3444)	601 (2524)	0.39 (0.09)
	Skeletal abnormalities	583 (2448)	1166 (4896)	583 (2448)	5.14(1.22)
	Total Malformations (unclear whether skeletal)	452 (339)	1360 (1010)	908 (681)	0.4 (0.59)
	Total variations	452 (339)	1360 (1010)	908 (681)	0.2 (0.24)
External abnormalities	Abnormal appearance high dose	219 (920)	820(3444)	601 (2524)	1.26 (0.3)
	Proportion of litters with ext. malformed pups	22 (92)	197 (920)	219 (828)	13.55 (3.23)
Note: The first number is the data as calculated from the relevant study. The number in brackets is corrected for exposure time (i.e. continuous exposure is converted to 40 hrs a week by multiplying the concentrations by 40/168)					

1-methyl-2-pyrrolidone (NMP)

Table X21-11: NMP Selected Occupational endpoints: Thresholds and dose response					
Effects		Threshold		Dose response curve	
		Converted (mg/m^3)	Range of Applicability for Slope	Converted (mg/m^3)	Slope ($\%/mg/m^3$)
Spontaneous abortion or still birth	Live birth index	280	612.5	332.5	-0.01
	Early resorption	510	1575	1065	0.2
	Viability Index	280	612.5	332.5	-0.24
	Viability Index	280	612.5	332.5	-0.17
	Resorptions/dam	875	1925	1050	4.03
Reduced foetal growth	Lactation Index	280	612.5	332.5	-0.03
	Pup Body weight gain	280	612.5	332.5	NO DATA
	Litters liveborn; dead at day 4	280	612.5	332.5	13.47
	Offspring weight per litter	207	470	263	-0.02
	Reduced pup body weights	206	478	272	-0.03
	Fetal pup Bodyweight females	219	438	219	-0.04

Table X21-11: NMP Selected Occupational endpoints: Thresholds and dose response					
Effects		Threshold		Dose response curve	
		Converted (mg/m^3)	Range of Applicability for Slope	Converted (mg/m^3)	Slope ($\%/mg/m^3$)
	Fetal Pup Body weight changes	243	486	243	-0.01
Skeletal effects or abnormalities of the limbs	Skeletal Malformations	437.5	875	437.5	2.06
	Skeletal Variations	437.5	875	437.5	0.40
	Extra 13th Rib	500	1000	500	0.38
	Extra 13th Rib	875	2917	2042	0.07
Foetal anomaly	Fetal Malformations	510	1575	1065	0.2
	External Malformations	437.5	875	437.5	2.44
	Visceral Malformations	437.5	875	437.5	1.46
	Visceral Variations	875	1312.5	437.5	1.9
	Total variations	875	2917	2042	0.03
	No Effects	>360			

X21.4 Relevant sectors, uses and operations

X21.4.1 General overview on uses

The main uses of DMAC, DMF and NMP are summarised in the following table. The main use of aprotic solvents is in the production of other chemicals with other uses in textiles, coatings, paint strippers/cleaners and in electronics.

Table X21-12: Main uses of aprotic solvents			
Use	DMAC	DMF	NMP
Solvent for the production of other chemicals (such as agrochemicals and pharmaceuticals)	70%	50%	40%
Man-made fibres/textiles/artificial leather	25%	25%	-
Coatings	5%	Unknown	20%
Paint strippers/cleaners	<1%	Unknown	20%
Electronics	Unknown	Unknown	20%
Source: ECHA (2018): Analysis of the most appropriate regulatory management option: N,N-Dimethylacetamide; Dimethylformamide (DMF); N-methyl pyrrolidone (NMP). Available at: https://echa.europa.eu/documents/10162/f96ae430-bfba-f349-36aa-fd9cc13c4f01			

X21.4.2 N,N-dimethylacetamide (DMAC)

DMAC has a variety of uses similar to NMP and DMF (discussed in the following sections). The uses of DMAC include in: [739]

- Manufacture of agrochemicals, fine chemicals and pharmaceuticals;
- Manufacture of coatings for industrial purposes as a solvent;
- Manufacture of textiles. This includes in the production of man-made fibres;
- Manufacture of the production of dialyser membranes and polyimide resins which are used in film production; and
- Used in paint stripper products for dissolvation and the removal of paints and varnishes. These products are used in the metal industry and also by professional users.

X21.4.3 N,N-dimethylformamide (DMF)

The Annex XV proposal for a restriction of DMF discusses the current uses of DMF.[738] The substance is used in the pharmaceutical industry in research and development, in the supply chain of Active Pharmaceutical Ingredients (APIs), and in the supply chain of in-vitro diagnostic medical devices. The main purpose of DMF is its use in synthesis and crystallisation. DMF is also used in the production of polyurethane coated textiles. This includes artificial leather, footwear, medical mattress covers, and protection wear.

The substance is also used in the manufacture of non-metallic products for example in coating processes. DMF is also used in the production of perfumes and fragrances and is also used as an extraction agent in the petrochemical industry. The substance is also used as a laboratory reagent. Other uses discussed in the RMOA for aprotic solvents include use as an industrial cleaner; manufacture of man-made fibres; in paint strippers; in epoxy inks; and in wire and non-wire coatings.

X21.4.4 1-methyl-2-pyrrolidone (NMP)

NMP is used for a variety of uses which are discussed in the RMOA for aprotic solvents.[739] The substance is used in the manufacturing process of up-stream chemicals such as agrochemicals and is also used for the extraction and purification of acetylene, benzene and 1,3-butadiene. NMP is used in the pharmaceutical industry in the formulation of active pharmaceutical ingredients with 5 000-10 000 tonnes of NMP used for pharmaceutical production for 2016 in the EU.

In the manufacturing of plastics and rubber, the substance is used in the extraction and purification of butadiene and is also used in the production of speciality synthetic rubber products. Up to 270 tonnes of NMP in 2016 were used for semiconductor manufacturing, where the solvent is used as a manufacturing processing aid and as a solvent in dedicated coating formulations. DMF is used in the production of polymer based membranes and for the manufacturing process of para-aramid polymer with uses in special textiles. Other uses of NMP include in the production of positive electrodes for lithium ion batteries, as a laboratory reagent, as a solvent for wire-coating and as an industrial cleaner and as a paint stripper.

X21.4.5 Summary of relevant sectors

The sectors where exposure to these aprotic solvents may occur are summarised in the following table.

[738] ECHA (2018): Annex XV Restriction Report. Proposal for a Restriction. Dimethylformamide (DMF). Available at: https://echa.europa.eu/documents/10162/9aa67e9e-0adb-7eda-53f9-021b700889d9

[739] ECHA (2018): Analysis of the most appropriate regulatory management option: N,N-Dimethylacetamide; Dimethylformamide (DMF); N-methyl pyrrolidone (NMP). Available at: https://echa.europa.eu/documents/10162/f96ae430-bfba-f349-36aa-fd9cc13c4f01

Table X21-13: Relevent sectors of use		
Solvent	**CAS**	**NACE**
N,N-dimethylacetamide (DMAC)	127-19-5	C13: Manufacture of textiles C20: Manufacture of chemicals and chemical products C22.2: Manufacture of plastic products C21: Manufacture of basic pharmaceutical products and pharmaceutical preparations
N,N-dimethylformamide (DMF)	68-12-2	B06.: Extraction of crude petroleum C13: Manufacture of textiles C14.1: Manufacture of wearing apparel, except fur apparel C15: Manufacture of leather and related products C15.2: Manufacture of footwear C20: Manufacture of chemicals and chemical products C21: Manufacture of basic pharmaceutical products and pharmaceutical preparations C25.9: Manufacture of other fabricated metal products
1-methyl-2-pyrrolidone (NMP)	872-50-4	B06: Extraction of crude petroleum C13: Manufacture of textiles C20: Manufacture of chemicals and chemical products C21: Manufacture of basic pharmaceutical products and pharmaceutical preparations C22: Manufacture of rubber and plastic products C25: Manufacture of fabricated metal products, except machinery and equipment C26.11: Manufacture of electronic components C27: Manufacture of electrical products

X21.5 Exposed workforce

X21.5.1 Total number of exposed workers

Estimates identified from SUMER data in France

The numbers of exposed workers to aprotic solvents in France are reported in SUMER for NMP, DMF and DMAC. For NMP, there are 47,700 exposed workers and for DMF and DMAC (reported together) there are 33,200 exposed workers in France. In total for these three substances, there are 80,900 exposed workers in France. Breakdowns of the exposed workers (male/female and age) are as follows:

- DMF and DMAC: 24,800 males and 8,400 females exposed;
- DMF and DMAC: 5,300 workers between the age of 25 and 29; 7,500 workers between 30 and 39 years old; 13,100 workers between the ages of 40 and 49; and 6,400 workers who are 50 years old and above;
- NMP: 3,100 workers below the age of 25; 2,900 workers between the age of 25 and 29; 16,400 workers between the age of 30 and 39 years; 13,900 workers between the age of 40 and 49; and 11,400 workers who are 50 years old and above; and
- NMP: 33,000 males and 14,700 females exposed.

Extrapolating the figures for exposed workers for France to the EU gives a total number of workers exposed to DMAC, DMF and NMP of 622,121 exposed workers in the EU with 366,813 workers exposed to NMP and 255,308 workers exposed to DMF and DMAC. A breakdown of these figures is as follows for occupational exposure for reprotoxins:

- DMF and DMAC: There are 41,207 female workers of reproductive age (15-49 years) potentially occupationally exposed to DMF and DMAC with 204,246 male workers exposed; and
- NMP: There are 253,770 male workers and 85,913 female workers of reproductive age (15-49 years) occupationally exposed.

In total, there are 585,136 workers of reproductive age exposed to these three aprotic solvents in the EU.

X21.6 Exposure levels

X21.6.1 Exposure routes

Exposure to aprotic solvents can occur via inhalation and dermal routes of exposure.

X21.6.2 Current exposure levels

N,N-dimethylacetamide (DMAC)

The Annex XV dossier for DMAC discusses that during the manufacturing of DMAC, exposure is not likely. The highest exposure to DMAC would likely occur during maintenance operations, but there are no measurements currently available. Data is available for exposure in Europe from 2001, however the relevance to current exposure levels is stated to be unclear. For other uses of DMAC, it is also discussed that most exposures are likely to be below the indicative OEL.[740] The highest reported exposure is <19 mg/m^3 from other sources.

N,N-dimethylformamide (DMF)

Occupational exposure levels of DMF reported in the literature are summarised in the following table with data reported in the MEGA database. The highest exposure level measured for DMF is 7.3 ppm (22 mg/m^3) for wet spinning in 1999 in Germany. More recent exposure data reported in 2010 is an exposure level of 1.77 mg/m^3 in the preparation of formulations. From other sources, the highest reported exposure is <7 mg/m^3 for systemic, long term exposure.

[740] ECHA (2011): Annex XV- Identification of N,N-Dimethylacetamide (DMAC) as SVHC. Available at: https://echa.europa.eu/documents/10162/11fc0850-0f0a-4dbe-9caa-5f7c01dd4dfe

Table X21-14: Exposure concentrations of occupational exposure to DMF		
Study	**Sector/use**	**Measurements**
Chang H-Y et al (2005): Total body burden arising from a week's repeated dermal exposure to N,N-dimethylformamide. Occup Environ Med, 62, pp 151-156	Synthetic leather factory; Taiwan Copper laminate circuit board; Taiwan	Geometric mean 3.9 ppm; GSD: 1.91 ppm Geometric mean 4.49 ppm; GSD: 1.84 ppm
Lee J et al (2018): Prioritizing Type of Industry though Health Risk Assessment of Occupational Exposure to Dimethylformamide in the Workplace. Int. J. Environ. Res. Public Health, 15, 503	Textiles Leather and related Chemicals and related Basic pharmaceutical Rubber and plastic (Korea)	GM: 4.92 mg/m^3; GSD: 9.54 mg/m^3 GM: 3.27 mg/m^3; GSD: 4.86 mg/m^3 GM: 0.99 mg/m^3; GSD: 2.73 mg/m^3 GM: 0.06 mg/m^3; GSD: 0.27 mg/m^3 GM: 4.50 mg/m^3; GSD: 6.06 mg/m^3
SCOEL (2006): Recommendation from the Scientific Committee on Occupational Exposure Limits for N,N-dimethylformamide	Wrbitzky and Angerer (1998); Wrbitzky (1999), Germany): Acrylic fibre plant Finishing Dyeing Dry spinning Wet spinning Catenacci et al., 1984 (Italy) Workers in acrylic fibre plant Lauwerys et al., 1980 (Belgium) Fiorito et al., 1997 (Italy) Workers in synthetic leather factory Cirla et al., 1984 (Italy)	 4.1 ± 7.4 ppm; 8-h-TWA 1.42 ± 2.2 ppm 6.7 ± 5.4 ppm 6.4 ± 9.6 ppm 7.3 ± 10.2 ppm 4-8 ppm; 8-h TWA 4.5 (0.4-15.3) ppm 7 ± 0.7 (1.6-13) ppm; 6 ± 0.6 (0.7-12) ppm; 8-h TWA 7 (2.6-19) ppm, TWA
Taminco N.V. (2010): Annex to extended Safety Data Sheet, N,N-dimethylformamide. TDS51021/12-2005, Belgium. As discussed in ECHA (2012): Annex XV- Identification of Dimethylformamide (DMF) as SVHC.	Formulation of preparations (mixing or blending in batch process for formulation of preparations and articles)	1.77 mg/m^3 (inhalation)

1-methyl-2-pyrrolidone (NMP)

Occupational exposure levels in Germany for NMP are available through the MEGA database.[741] NMP airborne concentration levels have been measured in a variety of operations and sectors. The 95th percentile concentrations vary between below the quantification limit of the measurement to 96.4 mg/m^3. The highest exposure measurement (90th percentile) is 57 mg/m^3 for cleaning activities in the manufacture and processing of metals.

[741] IFA (undated): Data on exposures by substances. Available at: https://www.dguv.de/ifa/gestis/expositionsdatenbank-mega/expositionsdaten-aus-mega-in-publikationen/publikationen-nach-stoffen/index-2.jsp

Table X21-15: MEGA database exposure for NMP					
Operation	Sector	Use	Concentration (mg/m³)		
			50 percentile	90 percentile	95 percentile
Mixing, pressing	Chemical industry	Manufacture/processing of coating materials, glue, mastics	+ 0.4	4.5	6.2
Foaming	Manufacture and processing of plastics and plastic foam and rubber products	Manufacture of plastic and plastic foam and plastics and plastic foam, processing	+ 0.2	0.84	1.72
Processing, sanding	Processing and treatment of wood	Processing and treatment of wood	Below analytical quantification limit value	Below analytical quantification limit value	Below analytical quantification limit value
Surface coating, painting, coating	Manufacture and processing of plastics and plastic foam and rubber products	Plastics and plastic foam, processing; Manufacture of plastic foils:	+ 0.3	2	2.6
	Manufacture and processing of metals	Processing of liquid coating materials (liquid varnish coating)	+ 0.7	3.86	5.415
	Steel construction, Manufacture of machinery and vehicles	Manufacture of parts for motor vehicles and engines (automotive supply)	0.7	5.56	7.36
	Electrical engineering, Fine mechanics, Optics	Electrical engineering:	+ 0.2	1.22	1.965
	Woodworking, paper, paper industry	Processing and treatment of wood:	Below analytical quantification limit value	0.46	0.95
Cleaning	Manufacture and processing of metals	Manufacture and processing of metals, general	1.5	57	96.4
	Electrical engineering, Fine mechanics, Optics	Manufacture of fine mechanics, optics	0.95	11.9	12
Gluing	Textiles	Manufacture of shoes	+ 0.15	0.405	0.485
	Manufacture and processing of plastic and plastic foam and rubber products	Plastics and plastic foam, processing	0.85	6.15	8.625
Source: IFA (2010): MEGA evaluations for the preparation of REACH exposure scenarios for N-methyl-2-pyrrolidone (vapour). Available at: https://www.dguv.de/medien/ifa/en/fac/reach/mega_auswertungen/n_methyl_2_pyrrolidon_en.pdf					

Other reported exposure measurements for occupational exposure to NMP, from literature review are discussed in the following table. Measured air concentrations are generally between non detectable levels and 10 mg/m^3, although peak exposures were reported in 2000 of up to 280 mg/m^3 for paint strippers.

Table X21-16: Exposure concentrations of occupational exposure to NMP		
Study	**Sector/use**	**Measurements**
Haufroid V et al (2014): Biological monitoring and health effects of low-level exposure to N-methyl-2-pyrrolidone: a cross-sectional study. Int Arch Occup Environ Health., 87(6), pp 663-674	-	ND to 25.8 mg/m^3 (median 0.18 mg/m^3)
Nishimura S et al (2009): A Cross-sectional Observation of Effect of Exposure to N-Methyl-2-Pyrrolidone (NMP) on Workers' Health. Industrial Health, 47, pp 355-362	NMP used for cleaning on which liquid resin had been sprayed; Japan	Mean exposure from 0.14ppm to 0.16ppm
SCOEL (2007): Recommendation from the Scientific Committee on Occupational Exposure Limits for N-Methyl-2-Pyrrolidone	Removal of graffiti (Anundi et al., 1993; Anundi et al., 2000) Microelectronics (Beaulieu and Schmerber, 1999) Paint-strippers (Åkesson and Jönsson, 2000a)	Up to 10 mg/m^3 Up to 6 mg/m^3 and up to 280 mg/m^3 when NMP has been used at 80 ^{o}C Up to 280 mg/m^3 for peak exposures

The highest reported exposure from other sources (confidential data) is <9 mg/m^3 for systemic long term exposure and <15 mg/m^3 for local long term systemic exposure. The highest reported exposure reported in the Annex XV restriction dossier for NMP is 20.65 mg/m^3 for formulation.[742]

X21.7 Current Risk Management Measures (RMMs)

X21.7.1 N,N-dimethylacetamide (DMAC)

Risk management measures for reducing occupational exposure to DMAC are discussed in its REACH registration dossier. Closed systems are used for uses at industrial sites such as for PROCs 1-3. However, for uses by professional workers, the only discussed use is as a laboratory chemical where exposure would occur. This is the same case as for DMF. The recommended exposure controls and PPE for reducing DMAC exposure are described in the following table. This includes taking into account both inhalation and skin exposure.

[742] ECHA (2013): Annex XV Restriction Report. Proposal for a Restriction. N-methylpyrorolidone (NMP). Available at: https://echa.europa.eu/documents/10162/2a5f3a2e-6f9c-08ac-6e44-4e4792b5cba9

Table X21-17: Recommended RMMs for DMAC	
Respiratory protection	If ventilation is inadequate use gas filter (such as EN 14387 Type A) for gases/vapour of organic compounds with boiling points >65 °C
Hand protection	EN 374 chemical resistant gloves. For prolonged, direct contact (>480 minutes of permeation time) use butyl rubber with 0.7 mm coating thickness
Eye protection	Safety glasses with side-shields (such as EN 166)
Body protection	Dependent on activity and possible exposure. For example use of apron, protecting boots and chemical resistant suit (EN 14605 for cases of splashes or EN ISO 13982 for dust)
General safety and hygiene measures	Avoid contact with eyes, skin and clothing. Avoid the inhalation of vapour. Handle the substance in accordance with good industrial hygiene and safety practice. Immediately remove all contaminated clothing. Store work clothing separately
Source: ECHA (2018): N,N-dimethylacetamide REACH registration dossier. Exposure controls/personal protection. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15266/9	

X21.7.2 N,N-dimethylformamide (DMF)

Risk management measures for reducing occupational exposure to DMF are discussed in its REACH registration dossier. Closed systems are used for uses at industrial sites such as PROCs 1-3. The recommended exposure controls and PPE for reducing DMF exposure are described in the following table. These exposure controls and PPE take into account both dermal and inhalation exposure.

Table X21-18: Recommended RMMs for DMF	
Engineering controls	Ensure adequate ventilation especially in confined areas
Respiratory protection	In case of vapour formation: use a respirator with filter model A; Use self-contained breathing apparatus (EN 133) for higher concentrations
Hand protection	Solvent resistant gloves (such as butyl rubber or neoprene) that satisfy EU Directive 89/689/EEC and EN 374 standard
Eye/face protection	Use tightly fitting safety googles; face shield; respirator with a full face mask
Skin protection	Wear suitable protective equipment and complete suit protecting against chemicals
General safety and hygiene measures	Take note of occupational restrictions for women of child bearing age
Source: ECHA (2018): N,N-dimethylformamide REACH registration dossier. Exposure controls/personal protection. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15093/9	

X21.7.3 1-methyl-2-pyrrolidone (NMP)

Risk management measures for reducing occupational exposure to NMP are discussed in its REACH registration dossier. Closed systems are used for some uses by professional workers and this includes the following PROC codes:

- PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions;
- PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions; and
- PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions

The recommended exposure controls and PPE for reducing NMP exposure are described in the following table. These exposure controls and PPE take into account both dermal and inhalation exposure.

Table X21-19: Recommended RMMs for NMP	
Respiratory protection	If the OEL may be exceeded: Use EN 14387 Type A gas filter for gases/vapours of organic compounds with boiling point > 65 °C; use respiratory protection in case of aerosol/vapour release; for gases/vapours of organic compounds and solid and liquid particles use a combination filter such as EN 14387 Type A-P2
Hand protection	Use chemical resistant gloves (EN 374). For prolonged, direct contact: Butyl rubber with 0.7 mm coating thickness (Protection Index 6 with >480 minutes of permeation time as according to EN 374) For short term contact: Nitrile rubber (NBR) with 0.4 mm coating thickness or chloroprene rubber (CR) with 0.5 mm coating thickness for >30 minutes of permeation time according to EN 364 (Protective Index 2)
Eye protection	Safety glasses with side-shields (EN 166)
Body protection	Dependent on activity and possible exposure. For example use of apron, protecting boots and chemical resistant suit (EN 14605 for cases of splashes or EN ISO 13982 for dust)
General safety and hygiene measures	Handle in accordance with good industrial hygiene and safety practice. Females in early pregnancy must not be exposed to the substance and must not come into contact of the skin or be inhaled by pregnant women. Immediately take off contaminated clothing and wash contaminated clothing before reuse. Inspect gloves regularly and prior to each use and replace if necessary
Source: ECHA (2018): 1-methyl-2-pyrrollidone REACH registration dossier. Exposure controls/personal protection. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/15493/9	

X21.8 Market analysis

X21.8.1 N,N-dimethylacetamide (DMAC)

The socio-economic characteristics of the sectors in which DMAC exposure may occur are summarised below.

- C13: Manufacture of textiles;
- C20: Manufacture of chemicals and chemical products;
- C21: Manufacture of basic pharmaceutical products and pharmaceutical preparations; and
- C22.2: Manufacture of plastic products.

Number of SMEs in each sector

Table X21-20: Number and proportion of SMEs by size of enterprise and sector									
Sector	TOTAL	Micro		Small		Medium		Large	
	No. firms	No. firms	% of total	No. firms	% of total	No. firms	% of total	No. firms	% of total
C13									
C20	**29,590**	19,580	66%	6,240	21%	2,950	10%	830	3%
C21	**4,560**	2,240	49%	960	21%	820	18%	540	12%
C22.2	**54,220**	35,490	65%	13,050	24%	4,900	9%	780	1%
Source: Eurostat's Structural Business Statistics database									

Average turnover by size of enterprise

Table X21-21: Average turnover by sector and size of enterprise, 2016												
Sector	Micro			Small			Medium			Large		
	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m
C13												
C20	13,281	19,580	0.68	34,247	6,240	5.49	132,655	2,950	44.97	346,366	830	417.31
C21	3,682	2,240	1.64	8,768	960	9.13	26,346	820	32.13	230,936	540	427.66
C22.2	11,410	35,490	0.32	46,395	13,050	3.56	98,462	4,900	20.09	78,698	780	100.89
Source: Eurostat's Structural Business Statistics database												

R&D expenditure

Table X21-22: Business expenditure on R&D per sector (in € million), EU28		
Sector	Data availability	R&D expenditure (in €m)
C13		
C20	C20	6,659.7
C21	C21	9,958.9
C22.2	C22	2,371
Source: Eurostat Notes: EU28 totals do not include data for some member states, due to confidentiality.		

X21.8.2 N,N-dimethylformamide (DMF)

The socio-economic characteristics of the sectors in which DMF exposure may occur are summarised below.

- B06.1: Extraction of crude petroleum;
- C13: Manufacture of textiles;
- C14.1: Manufacture of wearing apparel, except fur apparel;
- C15: Manufacture of leather and related products;
- C20: Manufacture of chemicals and chemical products;
- C21: Manufacture of basic pharmaceutical products and pharmaceutical preparations; and
- C25.9: Manufacture of other fabricated metal products

Number of SMEs in each sector

Table X21-23: Number and proportion of SMEs by size of enterprise and sector									
Sector	TOTAL	Micro		Small		Medium		Large	
	No. firms	No. firms	% of total	No. firms	% of total	No. firms	% of total	No. firms	% of total
B06									
C13									
C14.1									
C15									
C20	**29,590**	19,580	66%	6,240	21%	2,950	10%	830	3%
C21	**4,560**	2,240	49%	960	21%	820	18%	540	12%
C25.9									
Source: Eurostat's Structural Business Statistics database									

Average turnover by size of enterprise

Table X21-24: Average turnover by sector and size of enterprise, 2016												
Sector	Micro			Small			Medium			Large		
	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m
B06												
C13												
C15												
C20	13,281	19,580	0.68	34,247	6,240	5.49	132,655	2,950	44.97	346,366	830	417.31
C21	3,682	2,240	1.64	8,768	960	9.13	26,346	820	32.13	230,936	540	427.66
C25.9												
Source: Eurostat's Structural Business Statistics database												

R&D expenditure

Table X21-25: Business expenditure on R&D per sector (in € million), EU28		
Sector	**Data availability**	**R&D expenditure (in €m)**
B06		
C13		
C15		
C20	C20	6,659.7
C21	C21	9,958.9
C25.9		
Source: Eurostat Notes: EU28 totals do not include data for some member states, due to confidentiality.		

X21.8.3 1-methyl-2-pyrrolidone (NMP)

The socio-economic characteristics of the sectors in which DMF exposure may occur are summarised below.

- B06.1: Extraction of crude petroleum;
- C13: Manufacture of textiles;
- C20: Manufacture of chemicals and chemical products;
- C21: Manufacture of basic pharmaceutical products and pharmaceutical preparations;
- C22: Manufacture of rubber and plastic products;
- C25: Manufacture of fabricated metal products, except machinery and equipment;
- C26.11: Manufacture of electronic components; and
- C27: Manufacture of electrical products

Number of SMEs in each sector

Table X21-26: Number and proportion of SMEs by size of enterprise and sector									
Sector	**TOTAL**	**Micro**		**Small**		**Medium**		**Large**	
	No. firms	**No. firms**	**% of total**	**No. firms**	**% of total**	**No. firms**	**% of total**	**No. firms**	**% of total**
B06									
C13									
C20	**29,590**	19,580	66%	6,240	21%	2,950	10%	830	3%
C21	**4,560**	2,240	49%	960	21%	820	18%	540	12%
C22	**61,910**	40,470	65%	14,810	24%	5,600	9%	1,030	2%
C25	**386,050**	316,850	82%	57,050	15%	10,840	3%	1,310	0%
C26.11									
C27	**46,530**	34,390	74%	8,130	17%	3,060	7%	950	2%
Source: Eurostat's Structural Business Statistics database									

Average turnover by size of enterprise

Table X21-27: Average turnover by sector and size of enterprise, 2016												
Sector	Micro			Small			Medium			Large		
	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m	Turnover /€m	No. firms	Ave. turnover/ €m
B06												
C13												
C15												
C20	13,281	19,580	0.68	34,247	6,240	5.49	132,655	2,950	44.97	346,366	830	417.31
C21	3,682	2,240	1.64	8,768	960	9.13	26,346	820	32.13	230,936	540	427.66
C22	13,300	40,470	0.33	51,000	14,810	3.44	108,995	5,600	19.46	133,618	1,030	129.73
C25	58,462	316,850	0.18	133,951	57,050	2.35	159,000	10,840	14.67	130,000	1,310	99.24
C26.11												
C27	5,688	12,200	0.47	14,643	3,900	3.75	59,377	2,280	26.04	952,917	1,320	721.91
Source: Eurostat's Structural Business Statistics database												

R&D expenditure

Table X21-28: Business expenditure on R&D per sector (in € million), EU28		
Sector	Data availability	R&D expenditure (in €m)
B06.1		
C13		
C15		
C20	C20	6,659.7
C21	C21	9,958.9
C22	C22	2,371
C25	C25	2,629.9
C26.11		
C27		5,674.9
Source: Eurostat Notes: EU28 totals do not include data for some member states, due to confidentiality.		

X21.9 Burden of ill health

X21.9.1 Cases of ill health

N,N-dimethylacetamide (DMAC)

To assess the potential cases of ill health, two exposure scenarios have been considered:

- Indicative OEL of 10 ppm (36 mg/m^3); and
- Highest reported exposure data of <19 mg/m^3

One effect, foetal weight has a threshold (19 mg/m^3) below the indicative OEL with a change of 0.05%. The difference between the indicative OEL and the threshold is 17 mg/m^3 which give rise to a change of 0.85%. To calculate cases of ill health, birth weights are categorised as follows:

- Low under 2.5 kg;
- Very low under 1.5 kg; and
- Extremely low under 1 kg

For each of these categories, the percentage of births of all EU births that would be within 0.85% above the band was calculated and the process is described in the following table. From this, it can be seen that 0.79% of all live births are between 2.5 and 2.6 kg and if subjected to a decrease in weight of 0.85% would be below 2 kg and thus move from being a normal body weight to a low body weight. The percentage of EU live births between 1.5 and 1.56 kg is 0.036% and would move from low to very low body weight with a 0.85% decrease in body weight. The percentage for very low to extremely low body weight is 0.0011%.

Table X21-29: DMAC – endpoint "decrease in foetal body weight/litter"			
Birth weight	**Extremely low**	**Very low**	**Low**
Definition	< 1.0 kg	1.0 - 1.5 kg	1.5 - 2.5 kg
Definition of band above	1.0 - 1.5 kg	1.5 - 2.0 kg	2.5 - 3.0 kg
Births in band above in 2015 (1)	31,991	72,768	944,468
Range in which a 0.85% decrease would move the birth to a lower weight	1.0 - 1.0085 kg	1.5 - 1.51275 kg	2.5 - 2.52125 kg
Difference between top and bottom of the range	0.0085 kg	0.01275 kg	0.02125 kg
Difference as % of the 0.5 kg band	1.7%	2.6%	4.3%
Number of births in EU in the band above in 2015	544	1,856	40,140
Number of births in EU in band above as % of total number of births in EU in 2015 (5.1 million)	0.011%	0.036%	0.787%
Source: Eurostat: Live births by birth weight and duration of gestation, RPA analysis *Notes: 1 based on Eurostat data for BG, CZ, IE, EL, ES, LT, HU, MT, PO, PT, RO, SK, FI, extrapolated for EU*			

Based on extrapolation of the SUMER data (DMF and DMAC) for France to the EU, there are 41,207 female workers of reproductive age (15-49 years) potentially occupationally exposed to DMAC. Presuming 2.83% of female workers give birth each year gives rise to 1166 children. The number of cases of ill health from the indicative OEL is presented in the following table.

Table X21-30: Number of foetal weight cases for exposure to DMAC for the OEL scenario				
Exposed female workers	**Births per exposed female worker /year**	**Cases due to Decrease in foetal body weight/litter Normal to low body weight**	**Cases due to Decrease in foetal body weight/litter Low to very low body weight**	**Cases due to Decrease in foetal body weight/litter Very low to extremely low body weight**
41,207	1166	9.173	0.424	0.124

N,N-dimethylformamide (DMF)

To assess the potential cases of ill health, two exposure scenarios are considered:

- Indicative OEL: 10 ppm (40 mg/m^3); and
- Highest reported exposure: <7 mg/m^3.

The indicative OEL and the highest reported exposure value are below the lowest threshold of 92 mg/m^3 for external abnormalities. There are no cases of reproductive effects to occupational exposure to DMF.

1-methyl-2-pyrrolidone (NMP)

To assess the potential cases of ill health, two exposure scenarios are considered:

- Indicative OEL: 10 ppm (40 mg/m3); and
- Highest reported exposure (cleaners): 57 mg/m^3

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