Scientific Committee on Health, Environmental and Emerging Risks (SCHEER)

Request for an opinion on toxicological reference values for certain organic chemicals emitted from squishy toys with regard to adopting limit values under the Toy Safety Directive 2009/48/EC

1. Background

The Toy Safety Directive 2009/48/EC requires that chemicals in toys must not jeopardise the health and safety of children when used in the intended or in a foreseeable way, bearing in mind the behaviour of children.[1, 2]

Investigations of squeezable toys made of polymer foams, such as toy animals, different food products, e.g. ice cream, cakes and fruit, or emojies, revealed that these so-called squishy toys can emit chemicals in quantities that may give rise to concern.[3, 4] Risk assessments considered that the risk characterisation ratio (RCR) was exceeded in several instances, sometimes more than 100-fold, and that the toys could thus not be considered as safe.

The risk assessments were prepared using diverging toxicological reference values for the chemicals emitted, thus leading to diverging RCRs. This concerned a number of amines, cyclohexanone, xylenes and dichloromethane as summarised in the following table.

Substance		**Toxicological reference values used for risk assessment, µg/m^3**		
Name	**CAS No**	**1**	**2**	**3**
N,N-dimethylaminoethanol	108-01-0	116	1160	1160
N,N-dimethylformamide	68-12-2	80	80	270
Triethylendiamine	280-57-9	24	240	240
Bis(2-(dimethylamino)ethyl)ether	3033-62-3	2	20	20
1,1,4,7,7-pentamethyl-diethylentriamin	3030-47-5	28	280	280
Cyclohexanone	108-94-1	410	9700	410
Xylenes	1330-20-7	125	250	500
Dichloromethane, methylene chloride	75-09-2	100	88000	-

The background on the derivation of the toxicological reference values can be taken from the annex.

1 Article 10(2) of the Toy Safety Directive 2009/48/EC. OJ L 170, 30.6.20019, p. 1. https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1568041444770&uri=CELEX:02009L0048-20181126

2 Annex II, Part III, Point 1 of the Toy Safety Directive.

3 Danish Environmental Protection Agency (2018) Analysis and risk assessment of fragrances and other organic substances in squishy toys. Survey of chemical substances in consumer products no. 165, August 2018. https://www2.mst.dk/Udgiv/publications/2018/08/978-87-93710-64-1.pdf

4 Swedish Chemicals Agency (2019) Enforcement of squishies. ENFORCEMENT 6/19. https://www.kemi.se/global/tillsyns-pm/2019/enforcement-6-19-squishies.pdf

2. Terms of reference

The SCHEER is asked:

1. To review the available data on the toxicity of the organic compounds in the above table.

2. To advise on a toxicological reference value for each organic compound in the above table based on the most relevant data, taking into account the reasoning for each toxicological reference value, possible additive effects and different routes of exposure. To advise whether EU-LCI values can be applied for long-term inhalation, exposure risk for children with an adjusting assessment factor to be determined.

3. To advise on how to derive limit values for these compounds in squishy toys under the Toy Safety Directive 2009/48/EC, if appropriate taking account of the exposure to these compounds from sources other than toys.

Timeline

Preliminary opinion – September 2020

Final opinion – late autumn 2020

ANNEX. Background on toxicological reference values, µg/m^3 for organic compounds emitted from squishy toys

Toxicological reference values used for risk assessment, µg/m^3		
General note regarding the amines below		
Additive effects for aliphatic amines with irritation properties: The aliphatic amines are a class of volatile, water-soluble chemicals with a wide variety of industrial applications and commonly used in the production of PUR foam production. The most apparent effect of inhalation of the aliphatic amines is the irritation of the mucous membranes of the eyes and respiratory tract. The group of aliphatic amines induced irritation of the eyes, nasal passage and the respiratory tract and the effects were consistent with all aliphatic amines in animal studies and in cases of human exposure. As the same irritating properties are consistent for all aliphatic amines and these are used with their individual purpose in PU foam production, these will have an additive irritant effect. In the examination of the emission of these aliphatic amines from squishies, 4 relatively large emissions of aliphatic amines were found. Another additive aspect to be considered, is the exposure of amines from other sources. For example, it may be other PUR materials such as mattresses, pillows or other toys that are based on PUR foam. When there are other known exposure sources of chemicals restricted in the TSD the normal procedure is to allocate 10 % of TDI (in this case DNEL) for toys. We therefore propose to use an assessment factor for the additive effect due to exposure from several amines and several sources, of 10.	In general, the eye irritancy potential of aliphatic amines tends to be transitory and is perhaps in most cases not the most suitable endpoint for potential limit setting due to the likelihood of non-permanent adverse effects. The irritancy potential to the upper airway of saturated aliphatic and alicyclic amines is related to the lipophilicity of the substance. The greater degree of lipophilicity then the greater the likelihood of significant irritation (Gagnaire et al. 1993). Water soluble amines are likely to be cleared in the nose while lipophilic amines are more likely to affect pulmonary receptors and cause changes in breathing rate. The log P of 1,1,4,7,7-pentamethyl-diethylentriamin is -2.1, and the log P of the other three amines is in the range of -0.34 to -0.55. There is likely to be a common mechanism for irritation that is concentration dependent, and therefore in calculating the DNELs assessment factors for continuous exposure and study duration are not justified. Gagnaire, F. et al., 1993. Sensory and pulmonary irritation of aliphatic amines in mice: A structure–activity relationship study. Journal of Applied Toxicology, 13(2), pp.129–135. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/jat.2550130210	The basis for the reference values we used in this report were gathered from various sources. For four substances, we obtained information on NOAEC values from the Reach registrations disseminated at the European Chemicals Agency's (ECHA's) website (https://echa.europa.eu) • dimethylaminoethanol • triethylendiamine • bis (2-(dimethylamino) ethyl) ether) • 1,1,4,7,7-pentamethyldiethylenetriamine

N,N-dimethylaminoethanol CAS No 108-01-0		
116	**1160**	**1160**
NOAEL: 8 ppm = 29 mg/m^3. AF1 interspecies animal to human: 2.5 only account for toxic dynamic differences and no toxic kinetic. AF2 Intraspecies human sensitivity: 10 AF3: Time scaling and duration of experiments: 1. As the primary effects seen are related to irritation properties of the mucous membranes of the eyes and respiratory tract, the effects are related to concentration and not the dose. Therefore, no time scaling is required. AF4: Additive effects of aliphatic amines: 10 The DNEL is therefore 0.116 mg/m^3 (116 µg/m$^{3)}$.	The REACH registration dossier references a paper describing the effects of dimethylethanolamine in acute, 2-week, and 13-week inhalation toxicity studies in rats (Klonne et al. 1987). The mean (±SD) chamber concentrations for DMEA on the 13-week study were 8 (±0.8), 24 (±1.2), and 76 (±2.6) ppm equivalent to 29, 88, and 277 mg/m3. The registrant concluded that DMEA acts primarily as an ocular and upper respiratory tract irritant and toxicant at vapour concentrations of 76 ppm, while 24 ppm or less produced no biologically significant toxicity in rats. Thus, 24 ppm (88mg/m3) was considered the no-observable-effect level from the study conclusion: DMEA acts primarily as an ocular and upper respiratory tract irritant and toxicant at vapour concentrations of 76 ppm, while 24 ppm or less produced no biologically significant toxicity in rats. Thus, 24 ppm was considered to be the no-observable-effect level. The Danish EPA however based the squishy DNEL on 8ppm (29mg/m3). On closer examination of the original study, 10 animals of each sex were examined. At 24ppm 8 animals of each sex had unremarkable observations and 2 animals of each sex had very mild rhinitis that did not warrant further histological evaluation. At 76ppm squamous metaplasia, degeneration of the respiratory epithelium, atrophy of the olfactory epithelium and microcysts in the respiratory epithelium were observed in a number of subjects. Statistically significant changes in body weight were only recorded in the 76ppm group. For respiratory irritation and systemic effects therefore, the NOEC of 24ppm appears to be justified. In the 2-week study, rats exposed to 98, 288, or 586 ppm DMEA for 9 days (6 hr/day) exhibited signs of adverse effects on the respiratory system at 98ppm. It is relevant that there is no substantial difference between the concentrations at which these effects occur in sub- acute or chronic studies. However transient corneal opacity occurred in the 24 and 76ppm groups at the end of the daily exposure, beginning approximately 2-3 weeks after initiation of exposures. The opacity regressed during the night-time non-exposure hours. This is consistent with the mechanism of amine vapour toxicity on the eye where vision returns to normal in a short time after exposure ceases and permanent effects do not occur. Vapour concentration of the causative amine is a major factor in the development of glaucopsia, and a concentration-effect relationship is usually evident. A correlation exists between the vapour concentration, degree of corneal oedema, corneal thickness and	Inhalation study on rats. NOAEC: 29 mg/m3. Uncertainty factors: • 2.5 – toxicokinetic differences between animals and humans • 10 intra-individual sensitivity Critical effect: Eye and respiratory irritation Reference: Substance registration dossier ECHA's website.

	subjective symptoms (Ballantyne 2004). Time scaling for length of study is therefore not considered appropriate. The DNEL should therefore be reviewed as follows: Point of departure 29mg/m3 based on the study NOEC for respiratory irritation AF1 interspecies animal to human: 2.5 (for local irritation effects) AF2 intraspecies, differences in human sensitivity: 10 AF3 duration of experiments: 1 Since there was no substantial difference in the concentration at which respiratory effects occurred in the 2 week and 13 week studies the effects can be seen as concentration dependent rather than dose dependent. The DNEL is therefore 1.160 mg/m3 for N,N-Dimethylaminoethanol (1160 µg/m$^{3)}$ Ballantyne, B., 2004. Glaucopsia. Toxicological Reviews, 23(2), pp.83–90. Available at: https://doi.org/10.2165/00139709-200423020-00003. Klonne, D.R. et al., 1987. Dimethylethanolamine: Acute, 2-week, and 13-week inhalation toxicity studies in rats. Toxicological Sciences, 9(3), pp.512–521.	

N,N-dimethylformamide (DMF) CAS No 68-12-2		
80	**80**	**270**
-	-	For the substance DMF, we did not use the NOEAC value from ECHA's dissemination site, since the reference value given for the general public refers to workers. Instead, we used a so-called LOAEC value (Lowest Observed Adverse Effect Concentration) for DMF from a report published by the Danish Environmental Protection Agency.[5] We subsequently adjusted the chosen NOAEC and LOAEC values by using uncertainty factors according to the recommendations in ECHA's guidance documents[6] for deriving reference values. Study on workers. LOAEC: 8 mg/m3. Uncertainty factors: • 10 –intra-individual sensitivity • 3 – LOAEC to NOAEC Critical effect: Eye and respiratory irritation Reference: Report from the Danish Environmental Protection Agency[7]

5 Report from The Danish Environmental Protection Agency. N, N-dimethylformamide. Evaluation of health hazards and proposal of a health-based quality criterion for ambient air. Environmental Project No. 1543, 2014

6 ECHA 2012, Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health.

7 N,N-dimethyl-formamide Evaluation of health hazards and proposal of a health-based quality criterion for ambient air Environmental Project No. 1543, 2014.

Triethylendiamine CAS No 280-57-9		
24	**240**	**240**
NOAEC: 6 mg/m3 AF1 interspecies animal to human: 2.5 only account for toxic dynamic differences and no toxic kinetic. AF2 Intraspecies human sensitivity: 10 AF3: Time scaling and duration of experiments: 1. As the primary effects seen are related to irritation properties of the mucous membranes of the eyes and respiratory tract, the effects are related to concentration and not the dose. Therefore, no time scaling is required. AF4: Additive effects of aliphatic amines: 10 The DNEL is therefore 24 µg/m3	Relevant data in the literature for this substance is limited. The vapour pressure of triethylenediamine is however low and the substance is a solid at room temperature. This explains why the test animals were exposed using vapour and by a nose only method. The NOAEC is not questioned since distinct irritation was observed at the 0.063mg/m^3 concentration in the study. There is no reason to suggest that the mechanism of action would be significantly different than for N,N-Dimethylaminoethanol. In other words, the effect is concentration dependent and assessment factors for study length and continuous exposure are not required. The DNEL calculation is therefore: NOAEC: 6 mg/m3 DNEL = NOAEC/(AF1 x AF2 x AF3) AF1 (interspecies animals to human) = 2.5 (for local irritation effects) AF2 (intraspecies, difference in human sensitivity) = 10 AF3 (duration of trial, subchronic to chronic exposure) = 1 DNEL = 6 mg/m3/(2.5 x 10 x 1) = 0.24 mg/m3 (240 µg/m3)	Inhalation study on rats. NOAEC: 6 mg/m3. Uncertainty factors: • 2.5 – toxicokinetic differences between animals and humans • 10 – intraindividual sensitivity Critical effect: Eye and respiratory irritation Reference: Substance registration dossier ECHA's website.

<table>
<tr><th colspan="3">Bis(2-(dimethylamino)ethyl)ether   CAS No 3033-62-3</th></tr>
<tr><th>2</th><th>20</th><th>20</th></tr>
<tr><td>LOAEC: 21 mg/m3.
AF1: interspecies animal to human: 2.5 only account for toxic dynamic differences and no toxic kinetic.
AF2: Intraspecies human sensitivity: 10
AF3: 3 LOAEL to NOAEL extrapolation
AF4: Time scaling and duration of experiments:
1. As the primary effects seen are related to irritation properties of the mucous membranes of the eyes and respiratory tract, the effects are related to concentration and not the dose. Therefore, no time scaling is required.
AF5: Additive effects of aliphatic amines: 10

The DNEL is therefore 2 µg/m3</td><td>Relevant data in the literature for this substance is limited and the original study is unavailable. Signs of irritation of the eye and respiratory tract were noted at the lowest concentration. In contrast to DMEA the effects, particularly on the eye, were not transitory. On this basis the use of the LOAEC as the point of departure for deriving the DNEL is reasonable. Irritation is considered concentration dependent.

The DNEL calculation is therefore:
DNEL = LOAEC/(AF1 x AF2 x AF3 x AF4)
AF1 (interspecies animals to human) = 2.5 (for local irritation effects)
AF2 (intraspecies, difference in human sensitivity) = 10
AF3 (duration of trial, subchronic to chronic exposure) = 1
AF4 (LOAEC for NOAEC extrapolation) = 3

DNEL = 1.5 mg/m3/(2.5 x 10 x 1 x 3) = 0.02 mg/m3 (20 µg/m3)</td><td>Inhalation study on rats. LOAEC: 1.5 mg/m3.

Uncertainty factors:
• 2.5 – toxicokinetic differences between animals and humans
• 10 – intraindividual sensitivity
• 3 – LOAEC to NOAEC

Critical effect: Eye and respiratory irritation

Reference: Substance registration dossier ECHA’s website.</td></tr>
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1,1,4,7,7-pentamethyl-diethylentriamin CAS No 3030-47-5		
28	**280**	**280**
LOAEC: 21 mg/m3. AF1 interspecies animal to human: 2.5 only account for toxic dynamic differences and no toxic kinetic. AF2 Intraspecies human sensitivity: 10 AF3: 3 for LOAEC to NOAEC extrapolation AF4: Time scaling and duration of experiments: 1. As the primary effects seen are related to irritation properties of the mucous membranes of the eyes and respiratory tract, the effects are related to concentration and not the dose. Therefore, no time scaling is required. AF5: Additive effects of aliphatic amines: 10 The DNEL is therefore 0.028 mg/m3	Relevant data in the literature for this substance is limited and the original study is unavailable. Signs of irritation of the eye and respiratory tract were noted at the lowest concentration. The study report provides more detail than is available for the preceding substance. Observed changes were indicative of nonselective localized irritation to tissues at risk by exposure to sufficient vapour concentrations of the test material. At 3ppm there was localised irritation of nasal cavity however no indication of the severity was given. The registrant does however imply that the irritant effects are concentration dependent and therefore it is likely that study duration is unlikely to be a significant factor in determining the DNEL. The AF for study duration is therefore not accepted. DNEL = LOAEC/(AF1 x AF2 x AF3 x AF4) AF1 (interspecies animals to human) = 2.5 (for local irritation effects) AF2 (intraspecies, difference in human sensitivity) = 10 AF3 (duration of trial, subchronic to chronic exposure) = 1 AF4 (LOAEC for NOAEC extrapolation) = 3 DNEL = 21 mg/m3/(2.5 x 10 x 1 x 3) = 0.28 mg/m3 (280 µg/m3)	Inhalation study on rats. LOAEC: 21 mg/m3. Uncertainty factors: • 2.5 – toxicokinetic differences between animals and humans • 10 – intraindividual sensitivity • 3 – LOAEC to NOAEC Critical effect: Eye and respiratory irritation Reference: Substance registration dossier ECHA's website.

Cyclohexanone CAS No 108-94-1		
410	**9700**	**410**
LCI values for a number of compounds are/have been produced independently by AgBB (Germany) and ANSES (France). Some of these values are the same (sometimes because they have a common source/origin), but many are different because of different methods used to derive them (even when they are based on the same source/origin). The starting list for the EU-LCI setting process was those compounds that have been given LCI values by AgBB and ANSES. Compounds that, for whatever reason, have identical or very similar (differing by 20% or less) ANSES and AgBB LCI values were immediately marked as 'ascribed' EU-LCI. If differing by 20% or less, the lowest LCI value for the given compound in the two lists was used as the 'ascribed' EU-LCI. However, in due course, these compounds will be re-evaluated using the EU-LCI agreed protocol to produce de novo 'derived' EU-LCI values. Cyclohexanone has an 'ascribed' EU-LCI value of 410 µg/m³. This value was set according to an older derivation procedure: OEL/100 (OEL: occupational exposure limit). Therefore, the EU-LCI for cyclohexanone = EU-OEL / 100.	The DNEL for cyclohexanone is taken directly from the EU LCI of 410µg/m3. This EU LCI is an 'ascribed' value which is not derived de novo but taken from an analogous substance in the ANSES and AgBB lists. The basis for the setting of the LCI or the analogous substance was not available at the time of writing this opinion. Cyclohexanone has not been assessed by the US EPA and therefore no reference concentration is available from this source. Since in the Danish EPA report, the critical endpoint is mucous membrane irritation, the DNEL should be based on this effect. The Scientific Committee for Occupational Exposure Limits reviewed the limits for cyclohexanone and concluded that a NOAEC of 102 mg/m3 for irritation to the mucous membranes of human volunteers and a LOAEL of 775mg/m3 in rabbits for systemic effects were the best available bases for proposing a limit of 40.8mg/m3. An uncertainty factor of 2 was applied to allow for the limitations of the studies on which the limit was based (SCOEL 1992). This has subsequently been adopted in Commission Directive 2000/39/EC as an indicative occupational exposure level for cyclohexanone. An occupational DNEL can be based on the indicative occupational exposure level (ECETOC 2010). Since this is for workers, this DNEL can be converted to a general population DNEL by adjusting for exposure time by applying the factors 8/24 and 5/7 resulting in a rounded DNEL of 9700 µg/m3. The Danish EPA DNEL while referencing the EU LCI, is at variance with other published EU limits. Unless sufficient additional justification can be provided for adopting a more conservative level, the DNEL of 410 µg/m3 should be corrected to 9700 µg/m3. SCOEL, 1992. Recommendation from the Scientific Expert Group on Occupational Exposure Limits for cyclohexanone, Available at: file:///Users/tomasi/Downloads/sum 17 new template WEB ready.pdf.	We used EU-LCI values as reference values for the calculation of risk for two substances: • xylene • cyclohexanone LCI (Lowest Concentration of Interest) describes health-related reference values, developed in the EU, for the emission of chemical substances from construction products.[8] We chose to use these reference values in our risk assessment as they relate to products which emit chemicals in the indoor environment (although there may be some differences between construction products and toys in terms of emission[9]). The two EU-LCI values we used in our risk assessment are lower than the references values given by the Reach registrants of the substances. Our choice of reference values was justified by the precautionary principle, as well as by the fact that the subject of this report is exposure to children via toys. Critical effect: Eye and respiratory irritation Reference: EU-LCI: 410 µg/m3 [10]

8 http://ec.europa.eu/growth/sectors/construction/eu-lci/about_en

9 http://publications.jrc.ec.europa.eu/repository/bitstream/JRC83683/eca%20report%2029_final.pdf

10 Report from The Danish Environmental Protection Agency. N, N-dimethylformamide. Evaluation of health hazards and proposal of a health-based quality criterion for ambient air. Environmental Project No. 1543, 2014

Xylenes CAS No 1330-20-7		
125	**250**	**500**
The values for the substances with neurotoxicity as the critical effect (ethylbenzene, xylenes, styrene) are established in the report Danish Environmental Protection Agency (2016d) based on the EU-LCI values for the substances. Further, for each of the substances, there has been paid regard to small children possibly being particularly sensitive to effects on the central nervous system and that small children at a given concentration in the air inhale a larger amount of substances compared to their body weight. For these substances, the described aspects have been included by applying an extra factor of 4 compared to the EU-LCI values (see Danish Environmental Protection Agency, 2016d). In relation to other effects, such as 54 The Danish Environmental Protection Agency / Analysis and risk assessment of fragrances and other organic substances in squishy toys mucous membrane irritation, children are not considered more sensitive than adults, as these effects depend on the dosage to which the mucous membrane is exposed. Danish Environmental Protection Agency (2016D). Kortlægning og risikovurdering af toluen og andre neurotoksiske stoffer i børneværelset. Kortlægning af kemiske stoffer i forbrugerprodukter nr. 145, 2016.	The DNEL used in the report is based upon the EU lowest concentration of interest (LCI) for the neurotoxicity endpoint but lowered by additional assessment factors as described in a survey and risk assessment of toluene and other neurotoxic substances in children's rooms published by the Danish EPA (Miljøstyrelsen 2016). The Joint Research Council of the European Commission identified neurotoxicity as the critical endpoint with a LOAEC of 62mg/m3 from occupational studies. By applying assessment factors of 4.2 for duration of exposure, 5 for extrapolation to the general population, 3 for extrapolation from a LOAEC to a NOAEC, and 2 to account for less than lifetime exposure. The rounded LCI value is therefore 500 µg/m3. The Danish EPA however considered further assessment factors were necessary for children as was the case with toluene. An assessment factor of 2 was applied to take account of the higher dose relative to bodyweight from inhalation, however this is only likely to have relevance for very young children (<1 year) since the default toxicokinetic assessment factor of 3.16 is unlikely to be exceeded for children over this age (Valcke & Krishnan 2014). For xylene, physiological modelling shows that there are no differences between adults and children (Pelekis et al. 2001).This additional assessment factor is not considered to be necessary. A further assessment factor of 2 was applied to address the potential for additional sensitivity for neurotoxicity, but this was a precautionary approach in the survey and is not generally adopted practice in other EU risk assessment arenas including cosmetics. As with toluene there is a lack of data addressing neurotoxicity in critical windows or periods of development, therefore the additional assessment factor while likely to be conservative, is not without some justification. The DNEL after applying the additional assessment factor for early life sensitivity is therefore reduced from 500 µg/m3 to 250 µg/m3. The DNEL is four times lower than the EU LCI due to the application of additional assessment factors for children to account for differences	We used EU-LCI values as reference values for the calculation of risk for two substances: • xylene • cyclohexanone LCI (Lowest Concentration of Interest) describes health-related reference values, developed in the EU, for the emission of chemical substances from construction products.[11] We chose to use these reference values in our risk assessment as they relate to products which emit chemicals in the indoor environment (although there may be some differences between construction products and toys in terms of emission[12]). The two EU-LCI values we used in our risk assessment are lower than the references values given by the Reach registrants of the substances. Our choice of reference values was justified by the precautionary principle, as well as by the fact that the subject of this report is exposure to children via toys. Critical effect: Neuro toxicity Reference: EU-LCI: 500 µg/m3 [13]

11 http://ec.europa.eu/growth/sectors/construction/eu-lci/about_en

12 http://publications.jrc.ec.europa.eu/repository/bitstream/JRC83683/eca%20report%2029_final.pdf

13 https://ec.europa.eu/growth/sectors/construction/eu-lci/values_en

	in toxicokinetics and life stage susceptibility. The use of an additional assessment factor for toxicokinetics is not supported by the literature but it is not unreasonable to apply an additional factor for life stage susceptibility. Therefore, the DNEL of 125 µg/m3 should be corrected to 250 µg/m3. Miljøstyrelsen, 2016. Survey and risk assessment of toluene and other neurotoxic substances in children ’ s rooms, Pelekis, M., Gephart, L.A. & Lerman, S.E., 2001. Physiological-Model-Based Derivation of the Adult and Child Pharmacokinetic Intraspecies Uncertainty Factors for Volatile Organic Compounds. Regulatory Toxicology and Pharmacology, 33(1), pp.12–20. Available at: http://www.sciencedirect.com/science/article/pii/S0273230000914363. Valcke, M. & Krishnan, K., 2014. Characterization of the human kinetic adjustment factor for the health risk assessment of environmental contaminants. Journal of Applied Toxicology, 34(3), pp.227–240.	

Dichloromethane, methylene chloride CAS No 75-09-2		
100	**88000**	**-**
Estimate for 10^{-6} cancer risk, affects liver US EPA 2011. Methylene chloride. IRIS evaluation: https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~Ea6dIW:1	The DNEL of 100µg/m^3 used in the risk assessment is based upon the inhalation unit risk of 1 x10^{-8} per µg/m^3 derived by the US EPA assuming that dichloromethane is carcinogenic with a genotoxic mode of action. Based on the US EPA risk assessment, the air concentration that would represent a 1x10^{-6} excess risk of cancer is therefore 100µg/m^3. The evidence for carcinogenicity in humans is however not conclusive. In rodent studies, mice were more susceptible and this has been suggested to be due to reactive metabolites produced via a metabolic pathway catalysed by glutathione S transferase (GST). The GST pathway is found in human tissues but at much lower concentration levels. This conclusion is supported by the Scientific Committee on Consumer Safety Opinion on dichloromethane in cosmetics: The evidence does not suggest that dichloromethane shows cardiotoxicity or reproductive toxicity in man except at high levels. Although it is carcinogenic by inhalation in the mouse, factors have been identified which explain the higher susceptibility of mice compared to humans. Quantification of the risk to humans by modelling and comparison of the toxicokinetics indicates that the cancer risk that dichloromethane may pose would be negligible. (SCCS 2015) The Scientific Committee on Occupational Exposure Limits (SCOEL) reviewed the toxicity of dichloromethane in an occupational context and classified the substance as SCOEL carcinogen group C, implying the existence of a practical threshold for carcinogenicity and decided to assign an occupational exposure level (OEL) based on non-cancer endpoints. An OEL (8 h TWA) of 100 ppm (353mg/m^3) was recommended for methylene chloride and for possible short-term prenarcotic effects, a STEL (15 min) was set to 200 ppm (706mg/m3) (SCOEL 2009). These values have been adopted as indicative occupational exposure levels in Commission Directive (EU) 2017/164. ECETOC indicates that an indicative occupational exposure level may be taken as a DNEL for workers (ECETOC 2010). The REACH registration dossier for dichloromethane uses these levels for workers and also provides a short-term inhalation DNEL for the general population of 353 mg/m3 and long-term inhalation DNEL of 88.3mg/m3 both derived from the SCOEL assessment. The DNEL based on the US EPA unit cancer risk estimation is therefore not supported by current opinion in the European Union and is considered to be extremely conservative by a factor of at least 800	-

	times. SCCS, 2015. Scientific Committee on Consumer Safety Dichloromethane Submission IV. , (March). SCOEL, 2009. Recommendation from the Scientific Committee on Occupational Exposure Limits for methylene chloride (dichloromethane) SCOEL/SUM/130, ECETOC, 2010. Guidance on Assessment Factors to Derive a DNEL, Brussels. Available at: http://www.cipd.co.uk/NR/rdonlyres/5A39DD36-C0A3-455D-AA96-EA2EB8F68CDA/0/GuidanceonAssessment.pdf	