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Ad-hoc study to support the initial establishment of the list of candidates for substitution as required in Article 80(7) of Regulation (EC) No 1107/2009

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Final report

Submitted by:

Food Chain Evaluation Consortium (FCEC)

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ABBREVIATIONS

A	Approved
a.s.	Active substance
AC	Acaricide
ADI	Acceptable daily intake
AFNOR	French standardisation office
AL	Algicide
AM	Arithmetic mean
AOEL	Acceptable operator exposure level
ARfD	Acute reference dose
AT	Attractant
B	Bioaccumulation
BA	Bactericide
BCF	Bioaccumulation factor
CA	Comparative assessment
CAS	Chemical registration number
CFS	Candidate for substitution
CIRAD	French Agricultural Research Centre for Development
CLP	Classification, labelling and packaging classification
COM	Commission
CPHR	Community plant health regime
CRD	Chemical regulation directorate
DAR	Draft assessment report
DB	Database
DE	Desiccant
DEFRA	UK department for Environment, Food and Rural Affairs
DFID	Department for international development
DG AGRI	DG Agriculture
DG ENTR	DG Enterprise and industry
DG ENVR	DG Environment
DG SANCO	DG Health and Consumers
DMS	Data Management System
DS	Dossier submitter
DT50	Time required for 50% dissipation of the initial concentration
DT90	Time required for 90% dissipation of the initial concentration
EC	European Commission
ECHA	European chemical agency
EEC	European Economic Community
EFSA	European food safety authority
EGNSSA	European Global Navigation Satellite System Agency
EL	Elicitor
ENEA	Italian research organisation
EP	European parliament
EPA	Environmental Protection Agency (USA)
EPPO	European and Mediterranean Plant Protection Organization
ESIS	European chemical Substances Information System
EU	European Union

F+B	Faust und Backhaus Environmental Consulting GbR
FAO	Food and Agricultural Organisation
FCEC	Food chain evaluation consortium
FMFACCP	German Federal Ministry on Food, Agriculture and Consumer Protection
FU	Fungicide
GMO	Genetically modified organisms
HB	Herbicide
IN	Insecticide
KEMI	Swedish Chemicals Agency
KO	Kick-off
MD	Master database
MO	Molluscicide
MRS	Master repository system
MS	Member state
NOAEL	No observed adverse effect level
NCA	National competent authority
NE	Nematicide
NRA	National risk agency
OIE	World organisation for animal health
PBT	Persistent, bioaccumulative & toxic
PHEA	Public health executive agency
POP	Persistent organic pollutant
P	Persistence
PPP	Plant Protection Product
PR	Pruning
PSD	UK Pesticides Safety Directorate (now CRD)
QA	Quality assurance
QC	Quality control
RAC	Rapporteurs of the Committee for Risk Assessment
RE	Repellant
REACH	Registration, Evaluation, Authorisation and Restriction of Chemical substances.
RMS	Rapporteur member state
RO	Rotencide
RoI	Registry of Intentions
S&PM	Seed and plant propagating material
SA	Safener
SCM	Standard cost model
SD	Standard Deviation
ST	Soil Treatment
SY	Synergist
T	Toxicity
ToR	Terms of reference
UBA	German Federal Environment Agency
VDMC	Van Dijk Management Consultants
VI	Virus Inoculation
vPvB	very Persistent, very Bioaccumulative
WHO	World Health Organisation
WTO	World trade organisation
XLS	Excel

EXECUTIVE SUMMARY

Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC, introduces comparative assessment and substitution to the regulatory process for plant protection products. This new approach will apply only to a sub-group of active substances – those identified as 'candidates for substitution' (CFS). The European Commission is to establish a list of CFS according to Article 80(7) of the Regulation which states that "*By 14 December 2014, the Commission shall establish a list of substances included in Annex I to Directive 91/414/EEC which satisfy the criteria set out in point 4 of Annex II to this regulation and to which the provisions of Article 50 of this Regulation shall apply*". After such a list has been established this new approach can be introduced.

Annex II of Regulation (EC) No 1107/2009 lists seven criteria (the term "condition" is being used in this study) and according to Article 24 of Regulation (EC) No 1107/2009 "*an active substance complying with the criteria provided for in Article 4 shall be approved, for a period not exceeding seven years, as a candidate for substitution if it meets one or more of the additional criteria laid down in point 4 of Annex II"*.

The conditions are based on the intrinsic hazardous properties of the active substance in combination with its use. An active substance will be considered as a CFS if any of the conditions are met.

The purpose of the study is to provide the Commission with an analysis of all active substances approved under Regulation (EC) No 1107/2009 and listed in the Annex to Commission Regulation (EU) 540/2011 (previously included in Annex I to Directive 91/414/EEC). It is a preliminary exercise listing substances that may qualify as CFS in support of the Commission's initial proposal of CFS.

The analysis has been conducted by comparing the agreed chemistry, toxicology and environmental fate and ecotoxicology endpoints, as specified in three main relevant documents:

- Latest version of the review report for approval of each active substance;
- Conclusions of the European Food Safety Authority (EFSA) on the relevant active substances (EFSA Conclusions); and,
- Where necessary, in the Draft Assessment Reports (DARs) and addenda and peer review reports provided by the Rapporteur Member State ;

against the relevant seven conditions specified in Annex II, point 4 of the Regulation (EC) No 1107/2009.

The study has been carried out by the Food Chain Evaluation Consortium (FCEC) from January to July 2013. Associated to this present report, the Data Management System consisting in a report repository database (Mendeley) and an Excel database forms the final deliverables of the study.

The methodology proposed by the FCEC study team to the Commission relied on the following principles:

- Only agreed data are considered for the assessment of individual active substances;
- Full traceability of the data and the possibility to go back to the review reports, the EFSA conclusions, and the DARs and addenda when required;
- An evolving and flexible data management system to allow data adjustments and to make the analysis useful for Commission services after the completion of the study;
- Presentation and communication of the results based on total transparency of all data sources and manipulations and in a user-friendly presentation.

More than delivering a preliminary list of CFS, the study team has developed a comprehensive and fully transparent data management system to allow further investigation and further fine-tuning of the listing of CFS.

Results in the Excel database are presenting all evidences for which a given active substance is qualifying as CFS.

The database consists of a list of 422 approved active substances until 31 January 2013. However, the analysis has been carried out in considering the list of active substances as structured in the Annex of Regulation (EU) 540/2011 leading to a total of 378 under consideration.

Depending on the chosen options a total of around 100 actives substances could be defined as CFS as they conform to, at least, one of the seven conditions in Annex II, chapter 4 of the Regulation (EC) No 1107/2009.

The conditions which define each active substance as CFS are clearly presented in the Excel database.

Individual listing of active substances qualifying for CFS conditions and sub-criteria are presented in annexes.

1. INTRODUCTION

The present document is the Final report for the assignment relating to the ad hoc study to support the initial establishment of the list of candidates for substitution as required in Article 80(7) of Regulation (EC) No 1107/2009.

This study is undertaken by the Food Chain Evaluation Consortium (FCEC) under the leadership of Arcadia International with inputs from van Dijk Management Consultants and Agra CEAS both partners of the consortium. In order to strengthen the risk assessment expertise of the research, the study team is completed by Dr Michael Faust from Faust & Backhaus Environmental Consulting and by the BiPRO Consulting human health team.

The study consists in addressing 7 conditions under which active substances (a.s.) may qualify as candidates for substitution (CFS). Therefore the research is based on 7 specific and independent analyses. A step by step approach and a close collaboration with the Commission have helped understanding the complexity of the issue and it allowed developing a Data Management System (DMS) for the operationalization of the conditions in order to respond to Commission requirements.

In addition to this introduction, this final report is structured as follows:

- **The second section** presents the objective of the study in the framework of the drafting of the preliminary list of CFS ;
- **The third section** recalls background information including the legislative framework, the substitution principle and the policy context related to implementation of the substitution principle ;
- **The fourth section** describes the Data Management System as well as the methodology that has been deployed over the course of the study ;
- **The fifth section** presents the results of the analysis for each of the seven conditions. For each condition, we explain the condition itself and we present the specific methodology to complete the analysis, the operationalization of the condition in the DMS and the results of the analysis ;

Associated to this report, the Data Management System consisting in a report repository database (Mendeley) and an Excel database forms the final deliverable of the study.

2. STUDY OBJECTIVES

The general objective of the study is to analyse all active substances (a.s.) approved under Regulation (EC) No 1107/2009[1] and listed in the Annex to the Commission Implementing Regulation (EU) No 540/2011 (previously included in Annex I to Directive 91/414/EEC) against the relevant conditions specified in Annex II, Point 4 of the Regulation (EC) No 1107/2009 to assess whether or not individual a.s. are qualifying as candidates for substitution (CFS) and identify the criteria why they qualify as CFS.

This study is a preliminary exercise listing candidates for substitution (CFS) in support of the Commission's initial proposal of CFS. According to Article 80(7) of Regulation (EC) No 1107/2009 "*the Commission shall establish a list of substances included in Annex I to Directive 91/414/EEC which satisfy the criteria set out in point 4 of Annex II to this Regulation and to which the provision of Article 50[2] of this Regulation shall apply*" by 14 December 2013.

The specific objectives of the study are as follows:

a) **Listing of all quantitative criteria with relevant endpoints under consideration under Annex II, Point 4 of Regulation (EC) No 1107/2009 for each individual active substance approved and listed in Annex to Regulation (EU) No 540/2011**.

b) **Proposing concrete options to substantiate the qualitative criteria** with respect to:
   - Interpretation of "significantly lower", "the majority of the approved active substances" and 'significant proportion of non-active isomers" ;
   - Definition of "group of substances", "use categories", "critical effects" and "use/exposure patterns" ;
   - Quantification of "high potential of risk to groundwater" and "very restrictive risk management measures".

c) **Developing proposals (options)** regarding the following conditions of Annex II, Point 4 of Regulation 1107/2009:
   - Its ADI, ARfD or AOEL is **significantly lower** than those of **the majority of the approved active substances** within **groups of substances**/**use categories** ;
   - There are reasons for concern linked to the nature of the **critical effects** (such as developmental neurotoxic or immunotoxic effects) which, in combination with the **use/exposure patterns**, amount to situations of use that could still cause concern, for example, **high potential of risk to groundwater**; even with **very restrictive risk management measures** (such as extensive personal protective equipment or very large buffer zones) ;
   - It contains a **significant proportion of non-active isomers** ;

[1] Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant production products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p.1

[2] In Article 50 of the Regulation (EC) No 1107/2009 an obligation for Member States is introduced to perform a comparative assessment when evaluating an application for authorisation for a plant protection product containing an active substance approved as a candidate for substitution.

- If, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, reviewed by the Authority, it is considered to have **endocrine disrupting properties** that may cause adverse effects in humans if the substance has not been excluded in accordance with the criteria laid down in point 3.6.5."[3]

d) **Producing a list of CFS for each option** and for each combination of options;

e) **Listing of active substances that meet one or more of the criteria of Regulation (EC) No 1107/2009 to be classified as a candidate for substitution** taking into account the various options under C).

[3] Regarding endocrine disrupting properties, and pending the adoption of these criteria, substances that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogenic category 2 and toxic for reproduction category 2, shall be considered to have endocrine disrupting properties during this study.

3. BACKGROUND

Since the early 1990's, Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products (PPP) on the internal market is probably the most prominent legislation of the European Union with respect to pesticides. This Directive aimed at harmonising the legislation regarding the placing of plant protection products on the market in the EU by establishing agreed criteria for considering the safety of active substances as well as the safety and effectiveness of the products in which they may be used.

Whereas administrating Council Directive 91/414/EEC decreased the number of active substances on the internal market, as well as the number of individual pesticides, the Commission reported in 2001[4] that reform of the regulatory framework was mainly necessary to reinforce the high level of protection of human health and the environment, increase transparency, define the role of the European Food Safety Authority, and avoid repetition of animal testing while improving the functioning of the internal market and enhancing the competitiveness of the European agrochemical industry.

In 2006, the Thematic Strategy on the sustainable use of pesticides was adopted by the Commission and the agreed Regulation (EC) No 1107/2009 to replace Directive 91/414/EEC was published by the EU on 24 November 2009 as Regulation (EC) No 1107/2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC[5] and 91/414/EEC. The so-called "pesticides package" contains this new Regulation 1107/2009 as well as three other pieces of legislation which comprise measures deriving from the Thematic Strategy:

- Framework Directive 2009/128/EC on the sustainable use of PPP[6] ;
- Regulation (EC) No 1185/2009[7] concerning statistics on pesticides. The key elements of this regulation are the provision of annual sales data and the provision of data every five years on usage on crops which are representative of those cultivated in the member state and of the pesticides used ;
- Directive 2009/127/EC[8] amending Directive 2006/42/EC with regard to machinery for pesticide application. It sets out standards that new equipment is expected to meet before it is placed on the market.

The Strategy is designed to further reduce the impact of pesticides, particularly plant protection products, on human health and the environment. Its specific objectives are to:

- Minimise the hazards and risks to health from the use of pesticides ;
- Improve controls on the use and distribution of pesticides ;

[4] On 26 July 2001, the Commission submitted a progress report to Council and Parliament on the functioning of Directive 91/414/EEC (COM (2001) 444).

[5] Council Directive 79/117/EEC of 21 December 1978 prohibiting the placing on the market and use of plant protection products containing certain active substances.

[6] Directive 2009/128/EC of the European Parliament and of the Council of 21 October 2009 establishing a framework for Community action to achieve the sustainable use of pesticides.

[7] Regulation (EC) No 1185/2009 of the European Parliament and of the Council of 25 November 2009 concerning statistics on pesticides.

[8] Directive 2009/127/EC of the European Parliament and of the Council of 21 October 2009 amending Directive 2006/42/EC with regard to machinery for pesticide application.

- Reduce the levels of harmful active substances, including through substituting the most dangerous with safer (including non-chemical) alternatives ;
- Encourage low input pest control by raising awareness, promoting good practice and consideration of possible application of financial instruments ; and
- Establish a transparent system for reporting and monitoring progress made in fulfilling the objectives of the Strategy, including the development of suitable indicators.

Whereas under Directive 91/414/EEC evaluations and decisions were essentially risk-based, Regulation 1107/2009 has introduced some significant changes such as introduction of "hazard-based cut-off criteria", which take into account only the intrinsic chemical properties of a pesticide. Active substances are evaluated based on the results of their classification (Table 1). This is in contrast to the former approval process, which considered not only hazard (toxicity), but also risk (how a product is used, when, where, how frequently, etc…).

Table 1 - Hazard based cut-off criteria

Human Health (toxicology)	*Environmental (ecotoxicology)*
Carcinogen category 1A & 1B unless negligible exposure[9]	PBT (Persistent, Bioaccumulative & Toxic)
Mutagen category 1A & 1B	POP (Persistent Organic Pollutant)
Toxic for Reproduction category1A & 1B unless negligible exposure[9]	vPvB (very Persistent, very Bioaccumulative)
Endocrine disruptor unless negligible exposure[9]	Endocrine disruptor

It is important to note that some questions remain over the interpretation of some of the criteria e.g. endocrine disruption[10], and the cut-off criteria will only take effect upon renewal of each active substance (most taking place between 2016 and 2019).

The Regulation 1107/2009 has also introduced new measures which aim to simplify the process by which pesticides are authorised (e.g. zonal authorisation). This is intended to speed up decision-making and ensure a level playing field within the zone in terms of pesticide availability. It aims to avoid unnecessary duplication of work and thus save registration costs for the industry.

Additionally, the new Regulation (EC) No 1107/2009 introduces provisions regarding "substitution".

[9] Product used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.

[10] The European Commission shall defined specific scientific criteria for the determination of endocrine disrupting properties to be adopted in accordance with the regulatory procedure with scrutiny.by 14 December 2013

3.1 The substitution principle

The concept of substitution of active substances and comparative assessment of plant protection products was not included in the Directive 91/414/EEC. However, some MS (e.g. Sweden) have experience in using the concept of comparative assessment and substitution since 1986. This experience relates to both substitutions of problematic products with other products or with non-chemical alternatives as well as changes in the formulations.

This principle is not new as it applies in different regulatory and risk management contexts. In chemicals legislations and risk management, the substitution principle refers to a policy principle that requires the replacement of hazardous (or potentially hazardous) chemical substances by less hazardous alternatives. A less common synonym is the *product choice principle*.

The approach taken by the EU is to establish a two-step tiered process in order to respect existing principles of registration of active substances at the EU level and commercial products at MS levels, as follows:

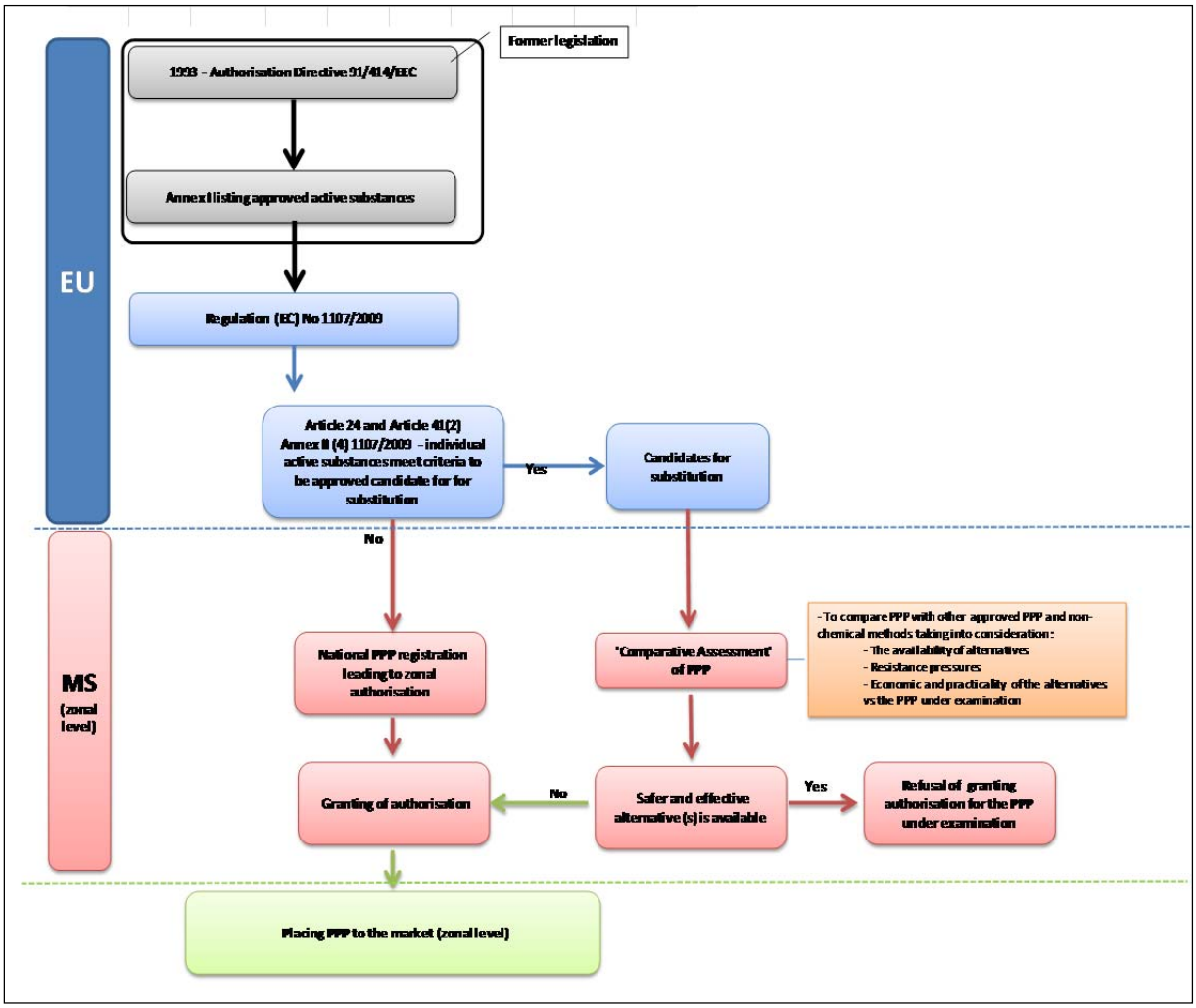
- Approved active substances listed in the Annex to the Commission Implementing Regulation (EU) No 540/2011 will be approved as "candidates for substitution" based on the criteria listed in Annex II, point 4 of Regulation 1107/2009, where for each active substance any of the following conditions are met:
    - *"Its ADI, ARfD or AOEL is significantly lower than those of the majority of the approved active substances within groups of substances/use categories ;*
    - *It meets two of the criteria to be considered as a PBT substance ;*
    - *There are reasons for concern linked to the nature of the critical effects (such as developmental neurotoxic or immunotoxic effects) which, in combination with the use/exposure patterns, amount to situations of use that could still cause concern, for example, high potential of risk to groundwater; even with very restrictive risk management measures (such as extensive personal protective equipment or very large buffer zones) ;*
    - *It contains a significant proportion of non-active isomers ;*
    - *It is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogen category 1A or 1B, if the substance has not been excluded in accordance with the criteria laid down in point 3.6.3 of Annex II of Regulation 1107/2009 ;*
    - *It is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 1A or 1B if the substance has not been excluded in accordance with the criteria laid down in point 3.6.4 of Regulation 1107/2009 ;*
    - *If, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, reviewed by the Authority, it is considered to have endocrine disrupting properties that may cause adverse effects in humans if the substance has not been excluded in accordance with the criteria laid down in point 3.6.5 of Regulation 1107/2009."*[11]

[11] Regarding endocrine disrupting properties, and pending the adoption of these criteria, substances that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogenic

- A comparative assessment (CA) shall be performed, at MS level, when (re-) evaluating an application for authorisation for a PPP containing an active substance approved as a candidate for substitution. This new process aims to compare a PPP with other approved PPP and non-chemical methods of control or prevention, and substitute the more 'hazardous' with a 'safer' alternative. Initiating a CA is considered when:
    - A review is required of an existing registered PPP, i.e. at renewal of the PPP authorization ;
    - An application for amendment of the registration of a PPP is received ;
    - An application for a new PPP is received.

  PPP containing an active substance categorised as CFS can therefore be approved under the new Regulation (EC) No 1107/2009 for up to seven years, and this authorisation is renewable. Furthermore, if e.g. they are needed for resistance management, they may remain on the market even if there is an available alternative.

Figure 1 - Substitution and comparative assessment under Regulation (EC) No 1107/2009



Source: Compiled by Arcadia International

category 2 and toxic for reproduction category 2, shall be considered to have endocrine disrupting properties during this study.

3.2 Policy context related to implementation of the substitution and comparative principles

The following provisions have been laid down in Regulation (EC) No 1107/2009.

Article 80(7) of Regulation (EC) no 1107/2009 mentions that "*by 14 December 2013, the Commission shall establish a list of substances included in Annex I to Directive 91/414/EEC which satisfy the criteria set out in Point 4 of Annex II to the Regulation and to which the provisions of Article 50 of this Regulation apply*".

Under Article 24 of Regulation (EC) No 1107/2009, active substances that meet certain specified health and environmental criteria (specified in Annex II (4) of 1107/2009) will be identified by the Commission as 'candidates for substitution'. For these active substances, approvals will be only granted for not more than seven years and any PPP containing that active substance will be required to undergo "comparative assessment" at Member State level (Article 50).

Another article of the Regulation 1107/2009 in which candidates for substitution' are mentioned is Article 41(2) stating that Member States may (no obligation) authorise a plant protection product under the mutual recognition procedure where it contains a candidate for substitution.

4. METHODOLOGICAL APPROACH

4.1 General considerations

Several experts have attempted to conduct assessments of the likely impact of the introduction of the hazard cut-off criteria and the substitution principle. They have all commented on the difficulty defining the list of active substances that will/could be banned under the new Regulation because some of the criteria are still to be finalised. In particular, as discussed above, there is no final and agreed definition of endocrine disruptors.

More particularly, the German Federal Ministry on Food, Agriculture and Consumer Protection (FMFACCP)[12], the Swedish Chemicals Agency (KEMI)[13], the Italian research organisation ENEA together with the Servizio Fitosanitario della Regione Emila-Romagna – Unità Technica Sviluppo Sostenibile ed Innovazione del Sistema Agro-Industriale[14] and the UK Pesticides Safety Directorate (PSD)[15] produced assessments of the likely substances that could be no longer approved under Regulation (EC) No 1107/2009 or/and that could be considered as candidates for substitution.

As regards substitution provisions, Annex II, point 4 of Regulation (EC) No 1107/2009 introduced qualitative criteria for each risk criterion for which a clear definition has not been set at this stage and which has to be clearly defined to proceed with a systematic and indisputable listing of candidates for substitution.

None of these EU expert assessments clearly presents how the conditions for approval of an a.s. as CFS have been interpreted. Instead e.g. the PSD report only mentions that "*the criteria finally agreed for identifying substances for substitution are very similar to those originally proposed by the Commission*" but doesn't provide any details.

On the basis of these preliminary analyses, the Commission and the FCEC study team considered that the methodological approach should rely on the following principles:

- **Only agreed data are considered** for the assessment of individual a.s.:
  - The study team has not performed any data interpretation ;
  - Full transparency of the assessment for each a.s. and for each condition ;
  - Only data included in 1) The EU pesticides database, 2) Review reports, 3) EFSA conclusions, 4) Annex of Regulation 1172/2008 for CLP classification;

[12] Federal Ministry on Food, Agriculture and Consumer Protection, Germany: Summary of assessment of the new pesticide legislation. Available at http://www.endure-network.eu/content/download/3979/29344/file/Summary%20of%20assessment%20of%20new%20EU%20PPP%20legislation%20in%20Germany.pdf

[13] Kemikalienenspektionen. "Interpretation in Sweden of the impact of "cut-off criteria" adopted in the common position of the Council concerning the Regulation of placing plant protection products on the market". 2008 Available at http://www.kemi.se/Documents/Bekampningsmedel/Docs_eng/SE_positionpapper_annenII_sep08.pdf

[14] ENEA, "Future availability of pesticides in the integrated pest management agricultural programme in Italy in accordance with the application of the new european regulation no 1107/2009 concerning the placing of plant protection products on the market: impact of the application of cut-off criteria and selection criteria for substances that are candidate for substitution", 2011, RT/2011/8/ENEA

[15] Pesticide Safety Directorate, now CRD, Chemicals Regulation Directorate, UK: Revised assessment of the impact on crop protection in the UK of the "cut-off criteria" and substitution provisions in the proposed Regulation of the European Parliament and of the Council concerning the placing of plant protection products on the market; 2008.

and 5) DAR reports and addenda have been considered. No other data sources have been considered.

- **Raw data traceability**. The origin of any raw values and raw end-points that are included in the database is mentioned in the Excel sheets and the corresponding sources are included in the Mendeley database. This approach allows for full traceability of the data and the possibility to go back to the review reports and the EFSA conclusions when required. For example when an aggregated value is provided, the reader can identify the different values that have been used for the aggregation;
- An **evolving and flexible data management solution to allow data adjustments** and to make the analysis useful for Commission services after the completion of the study. All data collected as part of the study as well as the Excel model have been transferred to the Commission at the end of the project. All models are designed to allow the Commission (or any authorised user) to implement:
  - Future updates of data for existing interpretations of conditions if e.g. new data become available ;
  - Changes to the parameters of the model to analyse the impact of different interpretations of each of the seven conditions on the final list of CFS (e.g. for the purpose of sensitivity testing).

The study raised several challenges that were identified in the initial stages of the study. They have been addressed in the methodology and during the performance of the project:

- **Relationship with stakeholders** (national authorities, EFSA, chemical industry, producers, and experts): This project is a scientific and a data analysis exercise where involvement of external stakeholder is not considered necessary at this stage of the process ;
- **Data management**: The list of substances to be drawn up as part of this project is based on a set of complex criteria that needs to be applied to a large database of substances in a robust, transparent and replicable manner. To do this, it is important to develop a robust data management system and process ;
- Related to the previous point, another challenge for this project lies in the **presentation and communication of the results**. Indeed, all of the findings, the research tools, database and underlying data need to stand up to the severe scrutiny that the outputs of this study will be subjected to. As a result, we have adopted a set of quality criteria for all elements of this project which the study team has adhered to throughout the contract. These include:
  - **Relevance of the database design** (including all entry fields) to the questions in the terms of reference ;
  - **Efficiency and effectiveness** of database design to ensure comprehensive data coverage and limited data manipulation ;
  - **Full transparency** of all data sources and manipulations ;
  - **User-friendly presentation** of the database itself and all its results to facilitate replicability of the analysis, an effective handover to the Commission at the end of the contract and the ability to extend and update the database as additional information becomes available.

4.2 The Data Management System (DMS)

On the basis of these preliminary considerations, the study team proposed to develop a Data Management System composed of two complementary modules:

- A Master Repository System (Mendeley). All documents and files (review reports and EFSA conclusions) have be downloaded from the different data sources and grouped in a bibliographic reference management database called the Master Repository System. This database includes all review reports, all EFSA conclusions and the Draft Assessment Reports and addenda that were required to complete the assessment.

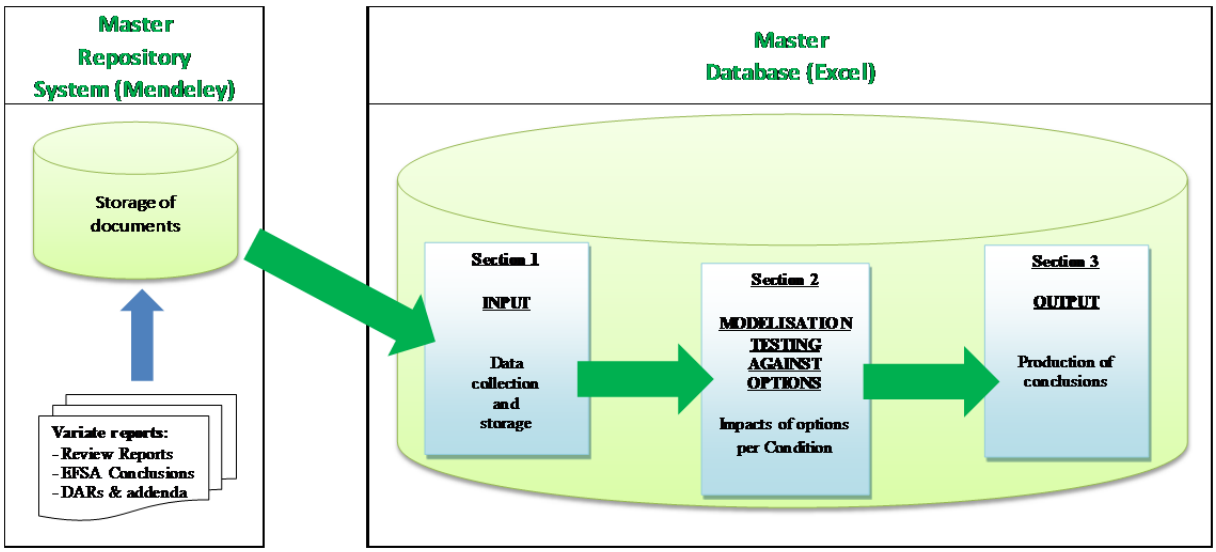
  The use of bibliographic reference management software is very helpful for:

  - Creating a structured database (library) of records ;
  - Identifying and removing duplicate records ;
  - Identifying new records when updating the searches ;
  - Managing the selection of records and recording selection decisions ;
  - Searching data values of specific end-points in the files.

- A Master Database (MD). All quantitative and associated qualitative data have been organised in an Excel DB.

  This database has been developed in a dynamic form meaning that functionalities to insert, delete and update records have been developed. This tool allows authorised DG SANCO users to use and update the DB after completion of the study, thus leaving a lasting legacy beyond the contract period.

Figure 2 - Overall structure of the Data Management System

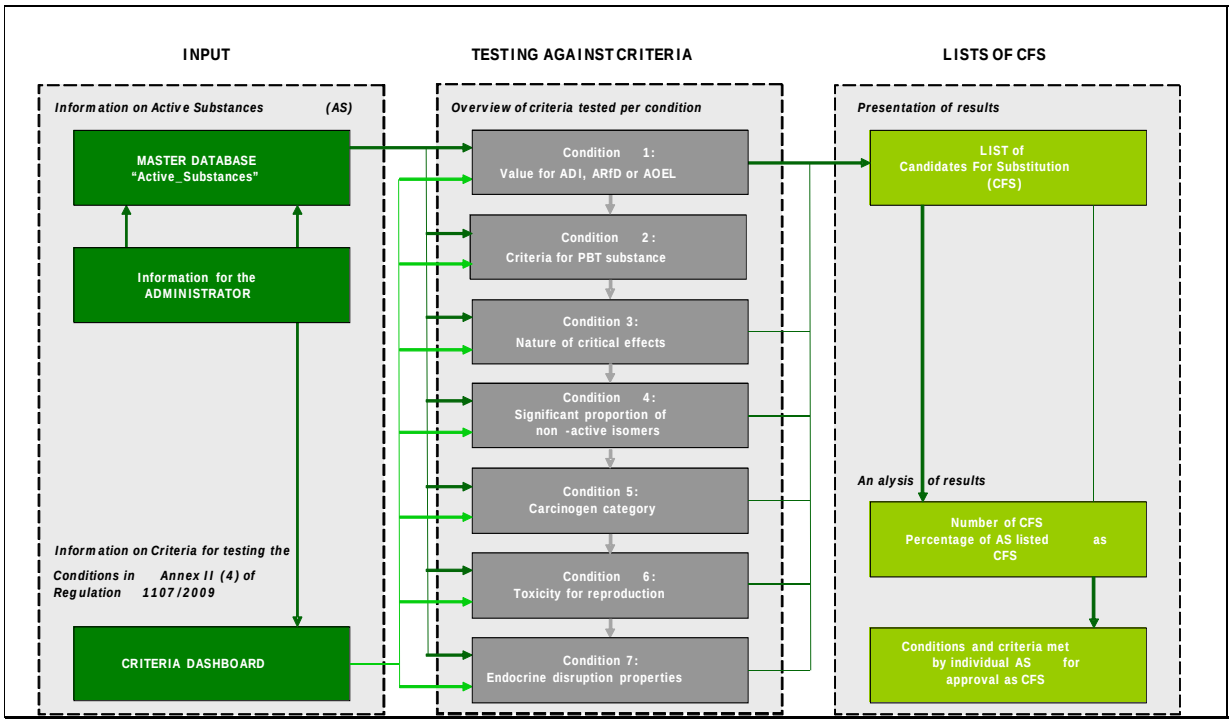


The Master Database is composed of three main components:

- Section 1 - Data Input: Data collection and data storage of all raw quantitative data required to identify candidates for substitution (CFS) per condition, as well as information regarding the seven conditions listed in Annex II (4) of Reg. 1107/2009. Data sources and origin are also mentioned ;
- Section 2 - Modelisation of options - Testing against criteria: for each condition, the criteria that need to be tested for assessing if a condition for approving an a.s. as CFS has been translated in algorithms ('instructions for the software') that can be combined to produce listings (per criteria and for any of the conditions) ;
- Section 3 - Data Output - Lists of CFS: Instructions of Section 2 are then applied against the database to produce listings of active substances that are candidates for substitution per and across conditions.

In order to ensure easy understanding of the Master Database structure, an interactive roadmap has been developed and integrated in the Excel tool. This roadmap refers to each of the individual sheets within the database and allows for easy access to all parts of the model. Whenever appropriate, colour codes have been used for distinguishing between the input, modelisation and outputs *sheets* as well as for distinguishing between different categories of *parameters* within one sheet. The latter is especially relevant for developing/using the reporting tool.

Figure 3 - Roadmap for the data model (support tool)



This database is to be considered as a centralised tool for all relevant information on criteria and decisions on options for establishing lists of approved CFS.

It has been defined on the basis of a set of quality criteria for all elements of this project which the study team has adhered to throughout the contract. These include:

- **Scope of the model in terms of a.s.**: the support tool centralises all information related to all a.s. with status "A(pproved)" and it foresees empty records already referring to the a.s. that are "P(ending)". Fully empty predefined records are available for future a.s. ;
- **Scope of the model in terms of Conditions**: the support tool centralises all information required for testing the criteria related to all seven conditions (hyphen 1 to 7) of the Annex II (4) of Reg. 1107/2009 ;
- **Quality assurance and quality control of raw data:** The collection of raw data leads to a large dataset in which most of the data are clearly identified. **However, in some cases differences/errors/non-understandable values have been found in the various reports. For these identified cases, we have reported the problem in the database to allow for further discussions aimed at reaching an expert agreement ;**
- **Transparency**: the implementation of the algorithms for testing the criteria for each condition is done in an easy to understand step-by-step way. Indeed, one of the objectives of the support tool is to provide in-sight into and transparency regarding how the different criteria and conditions affect the final list(s) of CFS. As such, we ensure that the support tool is not a "black box", but a genuine support for justifying decisions ;
- **Future proof:** the support tool first of all allows updating information related to active substances and adding information on pending and future a.s. (cf. supra). Furthermore, the model also allows for easy updating of the parameters related to the criteria that are used for assessing if the conditions in Annex II (4) of Regulation (EC) No 1107/2009 are met ;
- **User friendly**: in addition to being transparent and future proof, the model is structured in a very modular way, allowing for easy access and understanding of the functioning of each individual part of the model. The model allows for dynamic updates of the outcome (CFS lists); if needed, macros are used for ensuring that also more complex updates are correctly taken into account in the results of the modelling. Guidelines will be provided and training is foreseen for ensuring a smooth handing over of the model to the DG SANCO team ;
- **Decision support tool:** the tool is conceived as a decision support tool (cf. dashboard in 4) in the sense that it allows to have an immediate indication of the impact of alternative approaches for assessing the conditions in Annex II on the list(s) of approved CFS.

4.3 General approach to the work and data management

This section has a general overview of our approach to the data management work for this project. As mentioned before the core of this contract is related to data management and our approach focuses on developing a transparent, replicable and straight forward model that can be further tested and built upon beyond the contract period. The data management system consists of 3 components:

- A set of input sheets ;
- A set of sheets for testing the seven conditions (modelisation/analysis sheets) ;
- A set of sheets with the resulting lists of CFS (output sheets) ;

We describe each of these sheets in greater detail below.

Input sheets

The main input sheets are as follows:

1. The original *list of active substances* (cf. sheet "Active_Substances") and
2. The *overview of rules* (conditions and criteria) for creating the list(s) of CFS (cf. sheet "Dashboard") and guidelines for the database administrator, explaining e.g. abbreviations used, units for measures, etc.

List of active substances (a.s.)

This list contains *the name* of each of the a.s. as well as some *general information* (e.g. reference number (CAS), the chemical category and family, the rapporteur member state (RMS), the status under Regulation (EC) No 1107/2009).

Furthermore, *all information related to all of the criteria* that is used for testing the seven conditions for CFS approval is also added to the list of a.s. For each parameter and per individual a.s., a reference has been made to the source or source documents. Finally, any other relevant remark has been inserted in dedicated fields.

Overview of rules for creating the CFS lists ("Dashbord")

The dashboard provides a full overview of the rules that have been used for listing the CFS as well as an indication of the resulting list of CFS for each of the individual criteria and conditions:

Figure 4 - Snapshot of the dashboard

Dashboard

Overview of the conditions for approval as CFS and criteria for testing if any of the conditions is met.

This sheet provides an overview of how the support tool verifies if any of the 7 conditions in Annex II (4) of Regulation (EC) No 1107/2009 are met. For some conditions, Annex II (4) of Reg 1107/2009 already provides criteria with binary responses ("YES/NO"). They are indicated below as "static conditions". For other conditions, the criteria for testing if the conditions are met are mainly qualitative and need to be translated in quantative tests. For these conditions, the support tool contains a number of options for quantitative tests. These options are documented in detail in the respective sheets per condition.	**Resulting list of CFS based on single condition**	
	Number of CFS	**Percentage of a.s. approved as CFS**
Aggregated overall Conditions (see Sheet 'Final list of CFS')	**100**	**23.70%**
Condition 1: Value of ADI, ARfD or AOEL ("dynamic condition")		
Criteria applied for testing if an AS can be approved as CFS: — *Value contributing to categorisation as CFS:*		
- Is the substance's ADI significantly lower than those of the majority of the approved active substances within groups of substances/use categories ? — YES	13	3.08%
- Is the substance's ARfD significantly lower than those of the majority of the approved active substances within groups of substances/use categories ? — YES	6	1.42%
- Is the substance's AOEL significantly lower than those of the majority of the approved active substances within groups of substances/use categories ? — YES	14	3.32%
Decision rule:		
Significantly lower is currently defined as below the 5% Percentile of the AS for which the resp. ADI, ARfD or AOEL is available		
If one of the 3 criteria above is met, the AS can be approved as CFS. — *Overall outcome of criterion*	**26**	**6.16%**
Condition 2: Criteria for PBT Substance ("Static condition")		
Criteria applied for testing if an AS can be approved as CFS (cf. the 3 criteria for considering an AS as PBT substan — *Value contributing to categorisation as CFS:*		
- Can the active substance be considered as Persistent (P) ? — YES	121	28.67%
- Can the active substance be considered as Bioaccumulative (B) ?		
Decision rule : Is the bioconcentration factor higher than 2000 ? — YES	17	4.03%
- Can the active substance be considered as Toxic (T) ? — YES	170	40.28%
Decision rule:		
If two or more of the 3 criteria above are met, the AS can be approved as CFS. — *Overall outcome of criterion*	**78**	**18.48%**

Sheets for testing the criteria (per Condition) (analysis sheets)

The sheets for testing the criteria differ significantly from one condition to another.

For illustration purposes, we present on the next page the sheet related to the 'Carcinogen category' (Condition 5). As explained above, the implementation of the four criteria for testing if an a.s. can be approved as CFS based on this criterion is done by means of *a transparent step-by-step approach*. At the end, the outcome of each individual criterion or test is combined in order to have a combined outcome for this condition.

The *results at the level of the condition* consist of the following elements:

- Indication per individual a.s. *if this particular condition for CFS is met or not;*
- Presentation of the reason *why* a specific a.s. is approved as CFS;
- Indication of *how many a.s. are approved as CFS*, based on this condition;
- Indication of the *proportion of total a.s. (%)* that are approved as CFS, based on this condition.

Finally, an additional quality check has been performed, for highlighting any a.s. that would have been wrongly allocated to two categories[16].

[16] Provided that the input values are encoded based on drop down lists, the only possible error could exist in having an a.s. with an indication of both a 'classified category' and a 'to be classified category'; which is however most unlikely as an input error.

Figure 5 - Sheet for testing the criteria related to the Condition 5 – Category of Carcinogen

	A	B	C	D	E	F	G	H	I
1	**Annex II (4) of Reg 1107/2209, Condition 5 - Category of Carcinogen**						**Total number of CFS based on Category of Carcinogen**	**Number of CFS expressed as a % of AS with status "A"**	
3	**An active sustance shall be approved as a candidate for substitution if it is or is to be classified, in accordance with the provisions of Regulation (EC)N° 1272/2008, as carcinogen category 1A or 1B, if the substance has not been excluded in accordance with the criteria laid down in point**						**17**	**4%**	
4									
5	***Susbtance***	***CAS number***	**Test 1 for CFS: Is the substance classified as category 1A ?**	**Test 2 for CFS: Is the substance classified as category 1B ?**	**Test 3 for CFS: Is the substance to be classified as category 1A ?**	**Test 4 for CFS: Is the substance to be classified as category 1B ?**	**Overall outcome of criterion in Condition 5 - Category of Carcinogen**		**Quality check** *(Rule: one AS can maximum belong to one category)*
6			*(1 = YES; 0 = NO)*	*(1 = YES; 0 = NO)*	*(1 = YES; 0 = NO)*	*(1 = YES; 0 = NO)*	*(1 = CFS; 0 = NO CI*	*Reason for being CFS*	
53	Aluminium sulphate	10043-01-3	0	0	0	0	0	NO	0
54	Amidosulfuron	120923-37-7	0	0	0	1	1	To be classified as Carc. 1B	1
55	Amitrole (aminotriazole)	61-82-5	1	0	0	0	1	Classified as Carc. 1A	1
56	Ammonium acetate	631-61-8	1	0	0	0	1	Classified as Carc. 1A	1
57	Ampelomyces quisqualis strain AQ10	Not Applicable	1	0	0	0	1	Classified as Carc. 1A	1
58	Azadirachtin	11141-17-6 (aza	1	0	0	0	1	Classified as Carc. 1A	1
59	Azimsulfuron	120162-55-2	1	0	0	0	1	Classified as Carc. 1A	1
60	Azoxystrobin	131860-33-8	0	0	0	1	1	To be classified as Carc. 1B	1
61	Bacillus subtilis str. QST 713	Not Applicable	0	0	0	1	1	To be classified as Carc. 1B	1
62	Bacillus thuringiensis subsp. Aizawai strains ABT	Not Applicable	0	0	0	0	0	NO	0
63	Bacillus thuringiensis subsp. Israeliensis (serotyp	Not Applicable	0	0	1	0	1	To be classified as Carc. 1A	1
64	Bacillus thuringiensis subsp. Kurstaki strains ABT	Not Applicable	0	0	1	0	1	To be classified as Carc. 1A	1
65	Bacillus thuringiensis subsp. Tenebrionis strain N	Not Applicable	0	0	1	0	1	To be classified as Carc. 1A	1
66	Beauveria bassiana strains ATCC 74040 and GHA	Not Applicable	0	0	1	0	1	To be classified as Carc. 1A	1
67	Beflu			0	0	0	0	NO	0
68	Benal			0	0	0	0	NO	0
69	Benfl			0	0	0	1	Classified as Carc. 1A	1
70	Bensu			0	0	0	0	NO	0
71	Benta			0	0	0	0	NO	0
72	Benth			0	0	0	1	Classified as Carc. 1A	1
73	Benzo			0	0	0	1	Classified as Carc. 1A	1
74	Beta-			0	1	1	2	To be classified as Carc. 1A	2
75	Bifen			0	0	0	0	NO	0
76	Bifen			0	0	0	0	NO	0
77	Bifen			0	0	1	1	To be classified as Carc. 1B	1
78	Bispyribac	125401-75-4	0	0	0	0	0	NO	0
79	Bitertanol	55179-31-2	0	0	0	0	0	NO	0

For illustration purposes only

This table contains ***only dummy values*** for illustrating the functionning of this sheet.

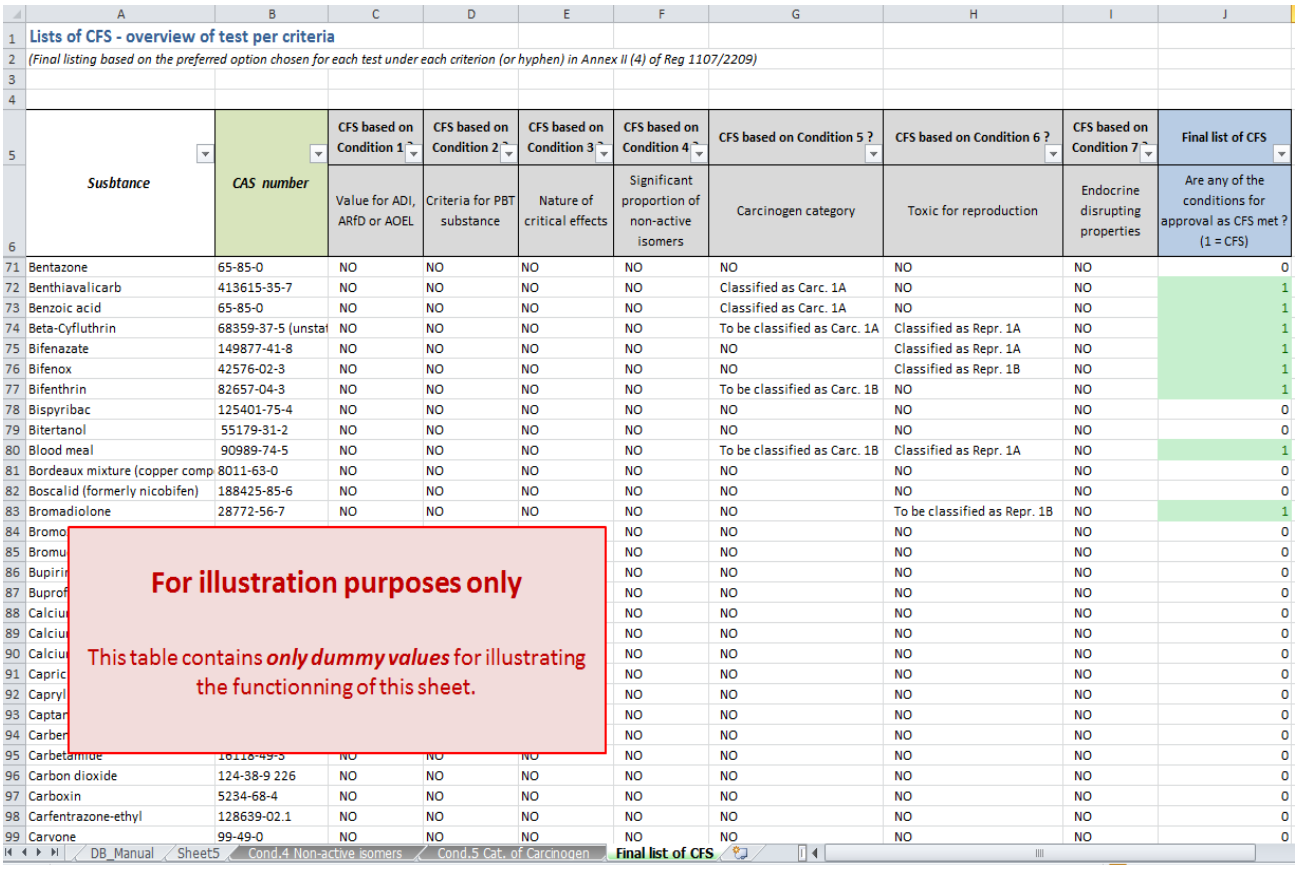
DB_Manual | Sheet5 | Cond.4 Non-active isomers | **Cond.5 Cat. of Carcinogen** | Final list of CFS

List of CFS

In a last step of the modelling, the outcome of the tests per criterion and condition are combined to obtain integrated list(s) of CFS. For illustration purposes, a first simplified approach has been implemented to show how the final outcome per condition can be integrated into a single list (see Figure 6).

The simplified approach presented in Figure 5 takes as a starting point that for each condition, the preferred set of criteria has previously been selected (this is especially relevant for the qualitative conditions that need to be translated into quantitative criteria), so that per conditions one single list of CFS has been created.

Figure 6 - Creation of integrated list of CFS



Lists of CFS - overview of test per criteria

(Final listing based on the preferred option chosen for each test under each criterion (or hyphen) in Annex II (4) of Reg 1107/2209)

Susbtance	CAS number	CFS based on Condition 1	CFS based on Condition 2	CFS based on Condition 3	CFS based on Condition 4	CFS based on Condition 5 ?	CFS based on Condition 6 ?	CFS based on Condition 7	Final list of CFS
		Value for ADI, ARfD or AOEL	Criteria for PBT substance	Nature of critical effects	Significant proportion of non-active isomers	Carcinogen category	Toxic for reproduction	Endocrine disrupting properties	Are any of the conditions for approval as CFS met ? (1 = CFS)
Bentazone	65-85-0	NO	NO	NO	NO	NO	NO	NO	0
Benthiavalicarb	413615-35-7	NO	NO	NO	NO	Classified as Carc. 1A	NO	NO	1
Benzoic acid	65-85-0	NO	NO	NO	NO	Classified as Carc. 1A	NO	NO	1
Beta-Cyfluthrin	68359-37-5 (unstat	NO	NO	NO	NO	To be classified as Carc. 1A	Classified as Repr. 1A	NO	1
Bifenazate	149877-41-8	NO	NO	NO	NO	NO	Classified as Repr. 1A	NO	1
Bifenox	42576-02-3	NO	NO	NO	NO	NO	Classified as Repr. 1B	NO	1
Bifenthrin	82657-04-3	NO	NO	NO	NO	To be classified as Carc. 1B	NO	NO	1
Bispyribac	125401-75-4	NO	NO	NO	NO	NO	NO	NO	0
Bitertanol	55179-31-2	NO	NO	NO	NO	NO	NO	NO	0
Blood meal	90989-74-5	NO	NO	NO	NO	To be classified as Carc. 1B	Classified as Repr. 1A	NO	1
Bordeaux mixture (copper comp	8011-63-0	NO	NO	NO	NO	NO	NO	NO	0
Boscalid (formerly nicobifen)	188425-85-6	NO	NO	NO	NO	NO	NO	NO	0
Bromadiolone	28772-56-7	NO	NO	NO	NO	NO	To be classified as Repr. 1B	NO	1
Bromo					NO	NO	NO	NO	0
Bromu					NO	NO	NO	NO	0
Bupirir					NO	NO	NO	NO	0
Buprof					NO	NO	NO	NO	0
Calciu					NO	NO	NO	NO	0
Calciu					NO	NO	NO	NO	0
Calciu					NO	NO	NO	NO	0
Capric					NO	NO	NO	NO	0
Capryl					NO	NO	NO	NO	0
Captar					NO	NO	NO	NO	0
Carber					NO	NO	NO	NO	0
Carbetamide	16118-49-3	NO	NO	NO	NO	NO	NO	NO	0
Carbon dioxide	124-38-9 226	NO	NO	NO	NO	NO	NO	NO	0
Carboxin	5234-68-4	NO	NO	NO	NO	NO	NO	NO	0
Carfentrazone-ethyl	128639-02.1	NO	NO	NO	NO	NO	NO	NO	0
Carvone	99-49-0	NO	NO	NO	NO	NO	NO	NO	0

For illustration purposes only

This table contains ***only dummy values*** for illustrating the functionning of this sheet.

DB_Manual | Sheet5 | Cond.4 Non-active isomers | Cond.5 Cat. of Carcinogen | Final list of CFS

4.4 Quality control of the data collection progress

A rigorous quality control process has been established to secure accuracy of the data sets. As already mentioned above, most of the data that have been inserted in the Excel database are agreed data. However we have identified a small percentage of endpoints for which conflicting values have been identified. As one of the main principles of the study is to work on agreed data only, we have documented these issues in the excel database without taking a final decision on the value to be used. This approach should allow experts and the Commission to identify these problems and then discuss them in order to reach an agreement on the value to be considered.

Each individual data point retrieved from the agreed data sources has been double checked to reduce the risk of errors during the analysis as a result of mistakes in transposing data from the original data source to the data analysis model.

Quality control on the data model has been performed by implementing testing phases to ensure that outputs were correct. The data models have been checked individually by both the QA team leader and the Data Input team leader.

5. CFS LISTING: ANALYSIS AND RESULTS

This section describes first the methodology applied for each individual condition. The methodology was developed based on a background analysis to define the best approach on the operationalization of the legal criteria from Annex II (4) for the identification of CFS.

Then statistical results are presented and annotated for each individual condition. Finally, the last part of this chapter summarises overall statistical results.

The aim of the exercise is to achieve a good differentiation between a.s. that qualify as CFS and the ones that are not qualifying for CFS. Disputable borderline cases should be avoided where possible. A priori, the availability of the necessary data from the relevant information sources, data distributions and the degree of correlation for the different criteria are unclear *ex ante*. Therefore, possible qualitative and quantitative interpretations of the legal criteria cannot be fixed from the beginning, but must be developed in an iterative process dependent on the outcome of the data mining exercise.

Proposals for the operationalization of the conditions have been developed on the basis of literature checks and brainstorming, first, within the study team and then with the Commission. NCAs, national and EU experts, and EU association experts have not been involved during that stage of the process.

5.1 Data availability

As of end of June 2013, 774 reports (all review reports that have been found in the EU Pesticides database and all EFSA conclusions present on the EFSA website) had been uploaded to the MRS.

Concerning EFSA conclusions, 248 reports were found on the EFSA website. All reports published on the EFSA website at the end of January 2013 were added to Mendeley as well as the EFSA conclusions for Straight Chain Lepidopteran Pheromones (SCLPs); Z,Z,Z,Z-7,13.16.19-docosatetraen-1yl isobutyrate; and Z-13-hexadecen-11-yn-1-yl acetate.

Additionally, the Draft Assessment Reports and addenda that have been consulted to complete the analysis have also been added to the Mendeley Database.

Modifications of the EU pesticides database and EFSA conclusions reports published after 01/02/2013 have not been integrated in the analysis presented below.

5.2 List of active substances under analysis

As of end of January 2013, the EU pesticides database contained 422 individual records which have been downloaded from the DG SANCO web site to create the initial version of the Master Database in Excel, of which:

- 390 a.s. in Part A of Regulation 540/2011. Part A contains 5 groups of substances which are including sub-forms of a given a.s. as follows:
    - The group of fatty acids (sub-form 230) lists 10 a.s. which are individually recorded in the EU pesticides DB and in the Excel DB;

  - The group of Straight Chain Lepidopteran pheromones (sub-form 255) lists 27 a.s. which are individually recorded in the EU pesticides DB and in the Excel DB;
  - The group of copper compounds (sub-form 277) lists 6 a.s. which are individually recorded in the EU pesticides DB and in the Excel DB;
  - The group of Quizalofop-P (sub-form 279) lists 3 a.s. which are individually recorded in the EU pesticides DB and in the Excel DB;
  - The group of parafin oils (sub-form 294) lists 3 a.s. which are individually recorded in the EU pesticides DB and in the Excel DB.
- 32 on Part B of Regulation 540/2011 (No group of substances in Part B);

This segmentation leads to a total of 378 a.s. under analysis (346 a.s. in Part A and 32 a.s. in Part B).

The Excel DB includes a specific column which repeats the reference number of the Annex of Regulation (EU) No 540/2011. For group of substances this number is repeated whenever required.

5.3 Background, analysis and results for Condition 1: "*Its ADI, ARfD or AOEL is significantly lower than those of the majority of the approved active substances within groups of substances/use categories*"

This section provides an examination of the data situation for ADI, ARfD and AOEL values, the corresponding options for the operationalization of Condition 1, and the resulting counts of CFS.

Available Data

The following Table 2 gives an overview on the data situation for ADI, ARfD and AOEL values that were available in the relevant information sources for a total 378 active substances that have been approved before the record data of 31 January 2013. Quantitative ADI, ARfD and AOEL values are available for 301, 178, and 307 approved active substances, respectively. For the remaining cases, the values were stated to be "not applicable" (around 20% for ADI and AOEL, and about 50% for ARfD entries).

Obviously, there are various types of reasons behind the qualitative information "not applicable", such as approved substances that are viruses or bacteria for instance. With respect to Condition 1, it seemed particularly important to clarify, whether there are cases where a quantitative value has not been set due to low toxicity, as this may have an impact on the assessment whether a value is significantly lower than for the majority of compounds. As a consequence, Review Reports and EFSA Conclusions were carefully checked for any explicit indications on reasons provided in the context of the statement "not applicable" and the phrases found were collected in a special Comment field in the MDB. From these pieces of information, no clear conclusive evidence results that for any of the substances an ADI, ARfD and AOEL was not set due to low toxicity. Further confirmation would require expert assessments on a case by case basis.

As a consequence, possible operationalization of the phrase "significantly lower than those of the majority" that are considered in this section always refer to those parts of approved substances for which quantitative ADI, ARfD or AOEL values were available in the relevant information sources.

Table 2 - Number of ADI, ARfD and AOEL data for approved active substances broken down by use categories (Approval status as of 31 January 2013)

Substances		ADI		ARfD		AOEL		All
		quantitative data	*not appl.*	quantitative data	*not appl.*	quantitative data	*not appl.*	
Approved a.s. (31 Jan 2013)		**301**	**77**	**178**	**200**	**307**	**71**	**378**
Use categories	AC	**20**	3	**15**	8	**20**	3	23
	AL	1	0	1	0	1	0	1
	AT	0	4	0	4	0	4	4
	BA	2	2	0	4	3	1	4
	DE	1	0	0	1	1	0	1
	EL	0	2	0	2	0	2	2
	FU	**91**	23	**57**	57	**93**	21	114
	HB	**115**	2	**52**	65	**115**	2	117
	IN	**57**	19	**48**	28	**57**	19	76
	MO	3	0	2	1	3	0	3
	NE	**7**	1	**6**	2	**7**	1	8
	OT	1	0	0	1	1	0	1
	PA	1	0	0	1	1	0	1
	PG	**25**	6	**14**	17	**28**	3	31
	PR	0	0	0	0	0	0	0
	RE	**6**	14	**5**	15	**5**	15	20
	RO	4	4	4	4	**7**	1	8
	SA	0	0	0	0	0	0	0
	ST	1	0	1	0	1	0	1
	SY	0	0	0	0	0	0	0
	VI	0	0	0	0	0	0	0
Assignment to use categories missing		0	7	0	7	1	6	**7**

Grouping

Condition 1 requires considering ADI, ARfD and AOEL values "*within groups of substances/use categories*". The EU Pesticides Database provides an allocation of active substances to one or more out of 21 different use categories. On the basis of the given relevant information sources, this was considered to be the most clear and solid reference for the necessary grouping of substances.

As an option, the Master Database created for this project allows clustering of two or more of the use categories, where this should be considered to be appropriate. However, the information sources evaluated for this project did not in themselves provide clear and well-reasoned arguments for such clustering.

Apart from grouping substances by use categories, the legal text of Condition 1 may also be interpreted in terms of other grouping criteria, such as chemical structures, physico-chemical

properties, or modes of action for instance. However, also for such alternative grouping approaches, the information sources evaluated for this project did not provide a solid ground and no consistently applicable criteria. In addition, with a view to the comparative assessment of CFS containing plant protection products, it seems questionable whether grouping criteria other than the intended uses of active substances could be really useful. This is because the comparative assessment refers to products with the same use(s) as specified in the application for authorisation (Article 50 of Regulation (EC) No 1107/2009). For these reasons, the option of setting up grouping criteria other than use categories was not further pursued. However, the DMS provides a clustering system that allows testing alternative groupings.

As a consequence, all further considerations in this section refer to the 21 use categories as defined by the information given in the EU Pesticides Database. A breakdown of all available data by these use categories gives the pattern shown in Table 2 above. For only 7 of the 378 approved active substances included in the analysis, an assignment to a use group is missing in the information sources checked. For the remaining 371 active substances, assignments to one or more out of 21 different use categories were found. For four of these categories all fields in the table are "empty" with no single substance assigned to them. Six further categories include only one or two different active substances each. Hence, a fraction that is smaller than the "majority" (less than 50%) cannot be defined and CFS Condition 1 is not applicable for these very small groups, whatever the specific threshold for the operationalization of the phrase "*significantly lower*" could be.

Therefore, the following considerations are confined to the 11 use categories which include more than two substances and hence allow the definition of a "*majority*".

Basic options for defining ADI, ARfD or AOEL values that are "*significantly lower than those of the majority*"

ADI, ARfD or AOEL values that are "significantly lower than those of the majority" may be defined in statistical or in toxicological terms. Statistically, a minority of significantly lower values may be defined as a certain fraction of a data set, such as a 5% percentile for instance (95% of the substances have higher values). Toxicologically, however, this does not necessarily mean that the 5% minority is also much more hazardous than the majority of substances. Whether this is true or not depends on the distribution of the data. If this is very narrow, the absolute quantitative differences may still be small and toxicologically insignificant.

As consequence, it suggested to consider both aspects, statistical and toxicological significance, in parallel, as detailed below. Regulatory acceptable dose levels, such as ADI, ARfD or AOEL, vary over orders of magnitude and the uncertainties and experimental variabilities that are inherent to these values are considerable. As a simple rule of thumb for the purposes of operationalizing Condition 1, it is therefore suggested to consider differences that are smaller than one order of magnitude as not being toxicologically significant. With the "*majority*" being defined by any value greater than the median (the 50% percentile), this means that a toxicologically significantly lower value would be one tenth or less of the median.

As a statistical measure, it has been proposed in the literature to define "*significantly lower than those of the majority*" in terms of a multiple of the standard deviation (SD) from the

mean (Rapagnani et al. 2011)[17]. This approach was therefore taken up in this study and tested as one of the available options. However, this approach has two major disadvantages. The first is a statistical one. The use of the SD as a measure for significant differences is based on the implicit assumption of a log-normal distribution of the data, which may be true or may not be true and hence requires examination of the actual data distributions. The second disadvantage is a matter of communication. To those who are not very familiar with statistics, it may be hardly understandable what it actually means, if for instance the ADI value of a substance is found to differ from the arithmetic mean of the log-transformed data by more than two times the SD.

As an alternative, we therefore suggest the simple use of percentiles (P) of the ranked data. If for instance an ADI value is found to not exceed the 5% percentile, this means that 95% of all substances have lower values. This is easy to communicate and independent from any distribution assumptions.

All three aforementioned ways of defining low ADI, ARfD or AOEL values (fractions of the median, multiples of the SD from the mean, and percentiles of a ranked data set) have one thing in common: they are depended from the actual distribution of data in a use category. Their meaning in terms of absolute values will change if substances are withdrawn or if new substances are approved for a certain use. As a fourth basic option, we therefore finally considered transferring such distribution dependent thresholds into fixed absolute values, such as an ADI of 0.001 mg/kg/d for instance.

In the following sections all four options are examined in detail. As a prerequisite, we first considered the necessary sizes of data sets and we examined the actual distributions of data in all major use groups. Given this basis, we specified all four options in terms of a few selected quantitative values and then determined the resulting counts of CFS.

Defining a minimum number of quantitative data for a reasonable application of Condition 1

The reasonable setting of a threshold value in terms of a percentile (P) implies the definition of a necessary minimum size of the data set, and vice versa. For example, if quantitative data are available for only 5 substances in a use category, every single active substance already accounts for 20% of all data. Under these conditions, the setting of the 5% percentile as a threshold value would be pointless, as it would affect ¼ of a substance, which is not considered as appropriate.

Given the data situation shown in Table 2, all further considerations on data distributions are therefore confined to 8 out of the 21 use categories (marked in bold green in Table 2). For 7 of these use categories (AC, FU, HB, IN, NE, PG, RE) a minimum number of 5 data is available for all three criteria (ADI, ARfD and AOEL). For the 8th use category (RO) this

[17] Rapagani MR, Maglulio M, Piccolo M, Nencini L, Galassi T, Mazzini F (2011) Future availability of pesticides in the integrated pest management agricultural programme in Italy in accordance with the application of the new European Regulation No. 1107/2009 concerning the placing of plant protection products on the market: Impact of the application of cut-off criteria and selection criteria for substances that are candidate for substitution. ENEA - Agenzia Nazionale per le Nuove Tecnologie, L'Energia e lo Sviluppo Economico Sostenibile Future, Report RT/2011/8/ENEA, Roma, Italy, available at http://www.dinamica-fp.it/centri/ra/docs/allegatoENEA.pdf (accessed 29.05.2013)

applies to the AOEL criterion only. Raising the threshold to a minimum of 10 data would exclude three further use categories (NE, RE, and RO) and hence reduce the exercise to 5 categories (AC, FU, HB, IN, PG).

Data Distributions

For defining distribution dependent thresholds in appropriate quantitative terms, it is necessary to examine the data distributions and to determine a number of descriptors of these distributions, such as minima and maxima, percentiles, median (50% percentile), mean, and SD. For the 7 selected use categories, these descriptors of the data distributions for ADI, ARfD, and AOEL values are compiled in the following tables 3, 4, and 5, respectively. In case of rodenticides, descriptions are provided for AOEL data only, as less than 5 data were available for ADI and ARfD (see above).

ADI, ARfD, and AOEL values range over several orders of magnitude. For an overview, they were therefore grouped in classes comprising 1 order of magnitude each. The resulting counts per class are given in absolute numbers in the tables 3 to 5. In addition, they are visualized as histograms of the relative counts for the five largest use categories and for all substances together (Figs. 7, 8, and 9).

In general, the distributions appear to be quite homogenous with no exceptional outliers. In many cases they seem to be compatible with the assumption of a log-normal distribution. In addition to the visual impression, this statement is supported by the fact that the 50% percentile (the median) often agrees quite well with the geometric mean (which corresponds to the arithmetic mean of the log-transformed data)[18].

However, there are clear exemptions from this rule, such as the distributions of the ADI and AOEL data for insecticides (IN) for instance, which are clearly left-skewed. This finding is important with respect to the definition of thresholds in terms of SD. As already mentioned above, Rapagani and co-workers (2011) have suggested to define a measure for "*significantly lower than those of the majority"* in terms of the arithmetic mean (AM) minus 1- or 2-fold standard deviation (SD) of the log-transformed data, which would correspond to the 16% and the 2.3% percentiles under the assumption of a normal distribution of the log-transformed data. The validity of such an approach can be affected by such skewed distributions.

As a consequence, the results of the distribution analysis strengthen the view, that the use of percentiles is the preferable alternative in comparison to the "AM minus *x*SD approach", not only because it is easier to communicate to the general public but also for statistical reasons. The tables 3, 4 and 5 therefore give the 1%, 2%, 5%, 10%, and 20% percentiles, provided that the data sets comprise a minimum of 100, 50, 20, 10, and 5 a.s., respectively.

In the following, the CFS counts resulting from the use of these percentiles as cut-off values are examined for all data sets; the "AM minus *x*SD approach" is applied for comparison only.

[18] In case of a perfect normal distribution mean and median are identical.

Table 3 - Distributions of ADI data

Parameter	ADI								
use category	ALL	AC	FU	HB	IN	NE	PG	RE	RO
class (upper limit in mg/kg bw/d)	***n***								
1.00E-05	0	0	0	0	0	0	0	0	
1.00E-04	0	0	0	0	0	0	0	0	
1.00E-03	13	1	2	6	5	**4**	1	0	
1.00E-02	83	**11**	23	33	18	2	5	1	
1.00E-01	**148**	7	**48**	**50**	**34**	1	**12**	**2**	
1.00E+00	51	1	16	24	0	0	6	2	
1.00E+01	6	0	2	2	0	0	1	1	
1.00E+02	0	0	0	0	0	0	0	0	
1.00E+03	0	0	0	0	0	0	0	0	
all	**301**	**20**	**91**	**115**	**57**	**7**	**25**	**6**	
	(mg/kg bw/d)								
lowest value	2.00E-04	1.00E-03	2.00E-04	4.00E-04	2.00E-04	4.00E-04	9.00E-04	6.00E-03	
1% percentile	4.00E-04	1.29E-03	9.20E-04	5.21E-04	3.12E-04	4.24E-04	1.40E-03	6.35E-03	
2% percentile	8.00E-04	1.57E-03	1.80E-03	7.48E-04	4.72E-04	4.48E-04	1.91E-03	6.70E-03	
5% percentile	2.00E-03	2.43E-03	3.00E-03	1.70E-03	1.00E-03	5.20E-04	3.00E-03	7.75E-03	
10% percentile	3.60E-03	2.95E-03	6.00E-03	3.24E-03	2.50E-03	6.40E-04	3.00E-03	9.50E-03	
20% percentile	1.00E-02	4.80E-03	1.00E-02	8.80E-03	5.00E-03	8.40E-04	1.00E-02	1.30E-02	
Median	**3.00E-02**	**1.00E-02**	**3.00E-02**	**3.00E-02**	**1.50E-02**	**1.00E-03**	**5.00E-02**	**2.00E-01**	
highest value	9.00E+00	1.70E-01	5.00E+00	9.00E+00	1.00E-01	6.00E-02	3.00E+00	3.00E+00	
geometric mean	**2.92E-02**	**1.18E-02**	**3.41E-02**	**3.07E-02**	**1.27E-02**	**2.58E-03**	**4.62E-02**	**1.38E-01**	
	log (mg/kg bw/d)								
arithmetic mean	-1.5332	-1.9294	-1.4672	-1.5086	-1.8960	-2.5878	-1.3352	-0.8589	
standard deviation	0.7542	0.4942	0.7007	0.7883	0.5865	0.7074	0.7875	0.9633	

Table 4 - Distributions of ARfD data

Parameter	ARfD								
use category	ALL	AC	FU	HB	IN	NE	PG	RE	RO
class (upper limit in mg/kg bw/d)	***n***								
1.00E-05	0	0	0	0	0	0	0	0	
1.00E-04	0	0	0	0	0	0	0	0	
1.00E-03	1	0	0	0	1	1	0	0	
1.00E-02	20	4	4	4	9	**3**	1	0	
1.00E-01	**91**	**9**	**26**	**28**	**24**	2	**10**	**3**	
1.00E+00	61	2	27	18	12	0	3	1	
1.00E+01	5	0	0	2	2	0	0	1	
1.00E+02	0	0	0	0	0	0	0	0	
1.00E+03	0	0	0	0	0	0	0	0	
all	**178**	**15**	**57**	**52**	**48**	**6**	**14**	**5**	
	(mg/kg bw/d)								
lowest value	1.00E-03	5.00E-03	4.00E-03	5.00E-03	1.00E-03	1.00E-03	1.00E-02	1.30E-02	
1% percentile	2.50E-03	5.00E-03	7.36E-03	6.53E-03	1.71E-03	1.08E-03	1.26E-02	1.57E-02	
2% percentile	4.54E-03	5.00E-03	1.00E-02	8.00E-03	2.41E-03	1.15E-03	1.52E-02	1.84E-02	
5% percentile	7.13E-03	5.00E-03	1.00E-02	9.10E-03	5.00E-03	1.38E-03	2.30E-02	2.64E-02	
10% percentile	1.00E-02	7.00E-03	2.00E-02	1.70E-02	6.75E-03	1.75E-03	3.45E-02	3.98E-02	
20% percentile	2.00E-02	1.00E-02	3.00E-02	3.00E-02	1.12E-02	2.50E-03	4.50E-02	6.66E-02	
Median	**1.00E-01**	**3.00E-02**	**1.00E-01**	**1.00E-01**	**5.00E-02**	**7.50E-03**	**8.00E-02**	**1.00E-01**	
highest value	1.00E+01	3.00E-01	1.00E+00	2.00E+00	1.00E+01	1.00E-01	1.00E+00	2.50E+00	
geometric mean	**8.00E-02**	**3.55E-02**	**9.88E-02**	**8.88E-02**	**5.80E-02**	**8.49E-03**	**8.64E-02**	**1.51E-01**	
	log (mg/kg bw/d)								
arithmetic mean	-1.0974	-1.4496	-1.0053	-1.0527	-1.2363	-2.0710	-1.0635	-0.8216	
standard deviation	0.6540	0.5478	0.5625	0.5921	0.7701	0.6646	0.4936	0.7506	

Table 5 - Distributions of AOEL data

Parameter	AOEL								
use category	ALL	AC	FU	HB	IN	NE	PG	RE	RO
class (upper limit in mg/kg bw/d)	***n***								
1.00E-05	1	0	0	0	0	0	0	0	1
1.00E-04	1	0	0	0	0	0	0	0	1
1.00E-03	10	1	3	4	3	**3**	0	0	1
1.00E-02	56	**14**	11	15	18	2	4	1	0
1.00E-01	**154**	3	**53**	**54**	**34**	1	**12**	**2**	**4**
1.00E+00	74	1	22	39	1	1	9	2	0
1.00E+01	9	1	4	2	1	0	3	0	0
1.00E+02	1	0	0	1	0	0	0	0	0
1.00E+03	1	0	0	0	0	0	0	0	0
all	**307**	**20**	**93**	**115**	**57**	**7**	**28**	**5**	**7**
	(mg/kg bw/d)								
lowest value	1.20E-06	1.00E-03	1.00E-03	6.00E-04	1.00E-03	8.00E-04	7.00E-03	1.00E-02	1.20E-06
1% percentile	6.12E-04	1.29E-03	1.00E-03	1.00E-03	1.00E-03	8.12E-04	7.00E-03	1.01E-02	2.15E-06
2% percentile	1.00E-03	1.57E-03	1.00E-03	1.00E-03	1.00E-03	8.24E-04	7.00E-03	1.02E-02	3.10E-06
5% percentile	2.50E-03	2.43E-03	4.48E-03	3.14E-03	1.40E-03	8.60E-04	7.00E-03	1.06E-02	5.94E-06
10% percentile	5.00E-03	2.77E-03	8.20E-03	7.00E-03	2.50E-03	9.20E-04	9.10E-03	1.12E-02	1.07E-05
20% percentile	1.00E-02	4.80E-03	1.54E-02	1.50E-02	6.78E-03	1.00E-03	2.70E-02	1.24E-02	5.36E-05
Median	**4.00E-02**	**9.50E-03**	**5.00E-02**	**6.00E-02**	**2.00E-02**	**5.00E-03**	**1.00E-01**	**1.50E-02**	**1.90E-02**
highest value	1.28E+02	1.50E+00	5.00E+00	1.40E+01	1.50E+00	3.00E-01	1.00E+01	1.00E+00	4.20E-02
geometric mean	**4.30E-02**	**1.15E-02**	**5.22E-02**	**5.60E-02**	**1.73E-02**	**5.63E-03**	**1.04E-01**	**5.67E-02**	**1.12E-03**
	log (mg/kg bw/d)								
arithmetic mean	-1.3670	-1.9376	-1.2824	-1.2515	-1.7623	-2.2492	-0.9836	-1.2466	-2.9525
standard deviation	0.8490	0.6602	0.7261	0.7391	0.6058	0.8512	0.7935	0.8231	1.7067

Figure 7 - Histograms of ADI data

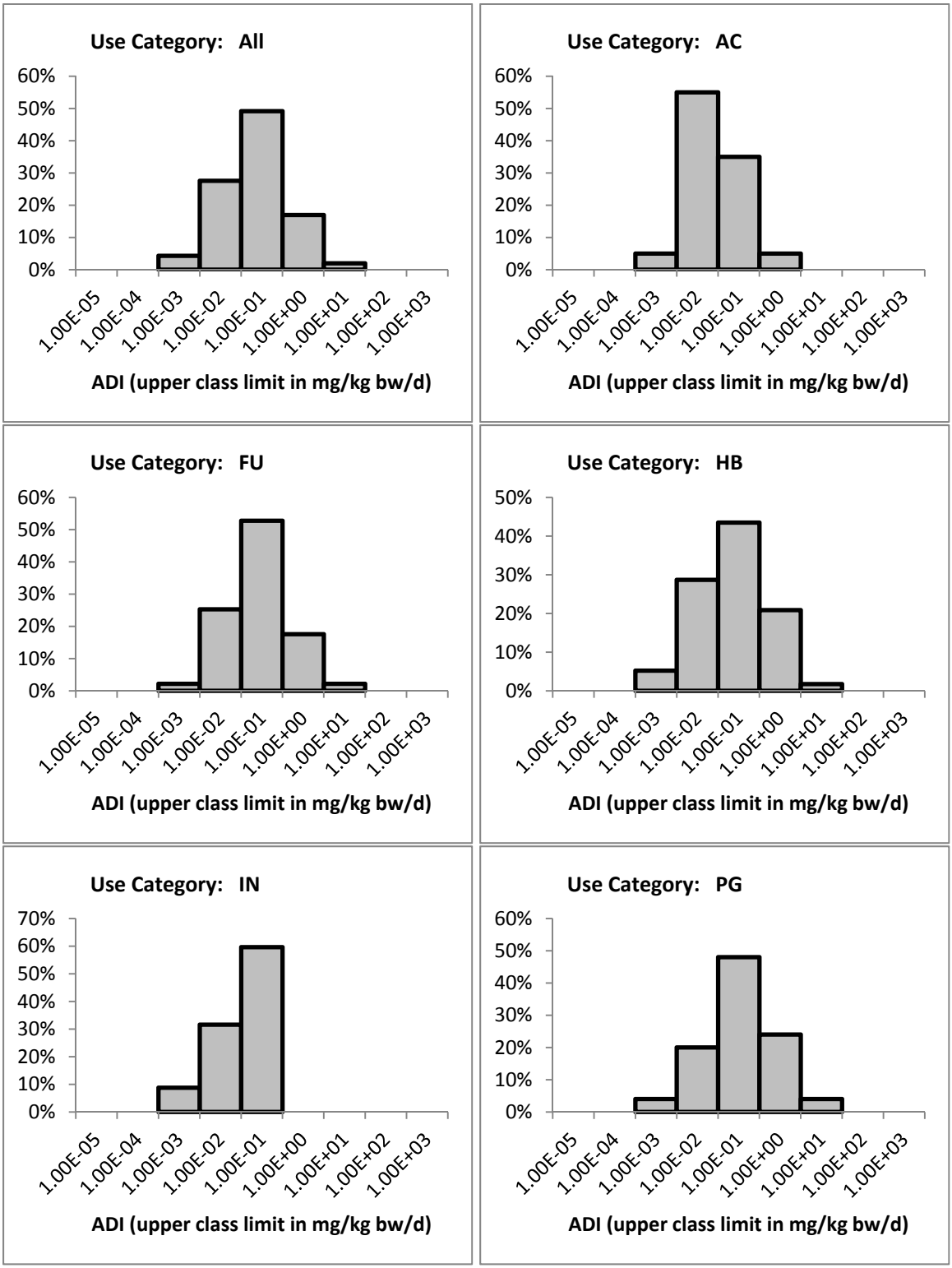


Figure 8 - Histograms of ARfD data

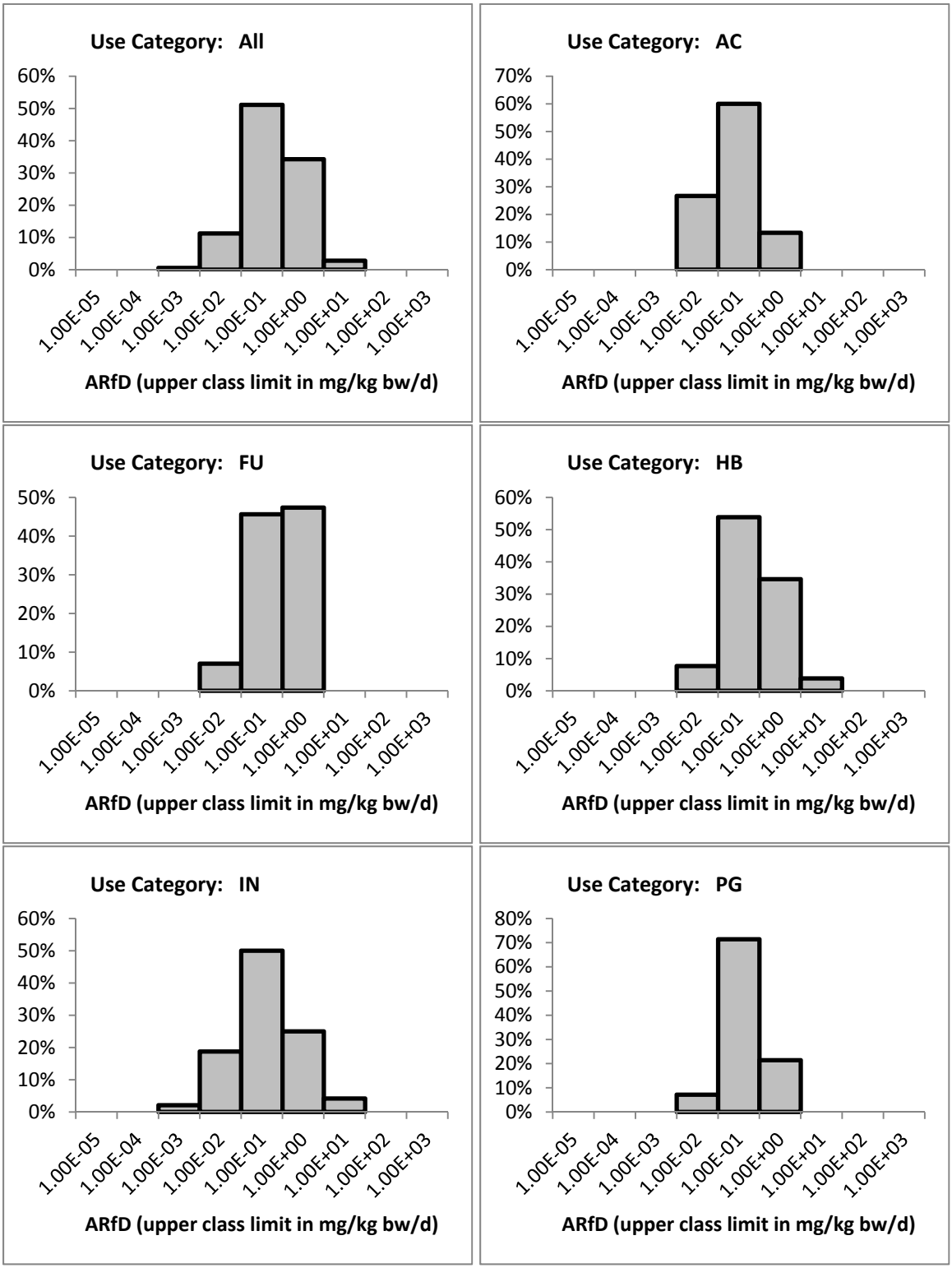
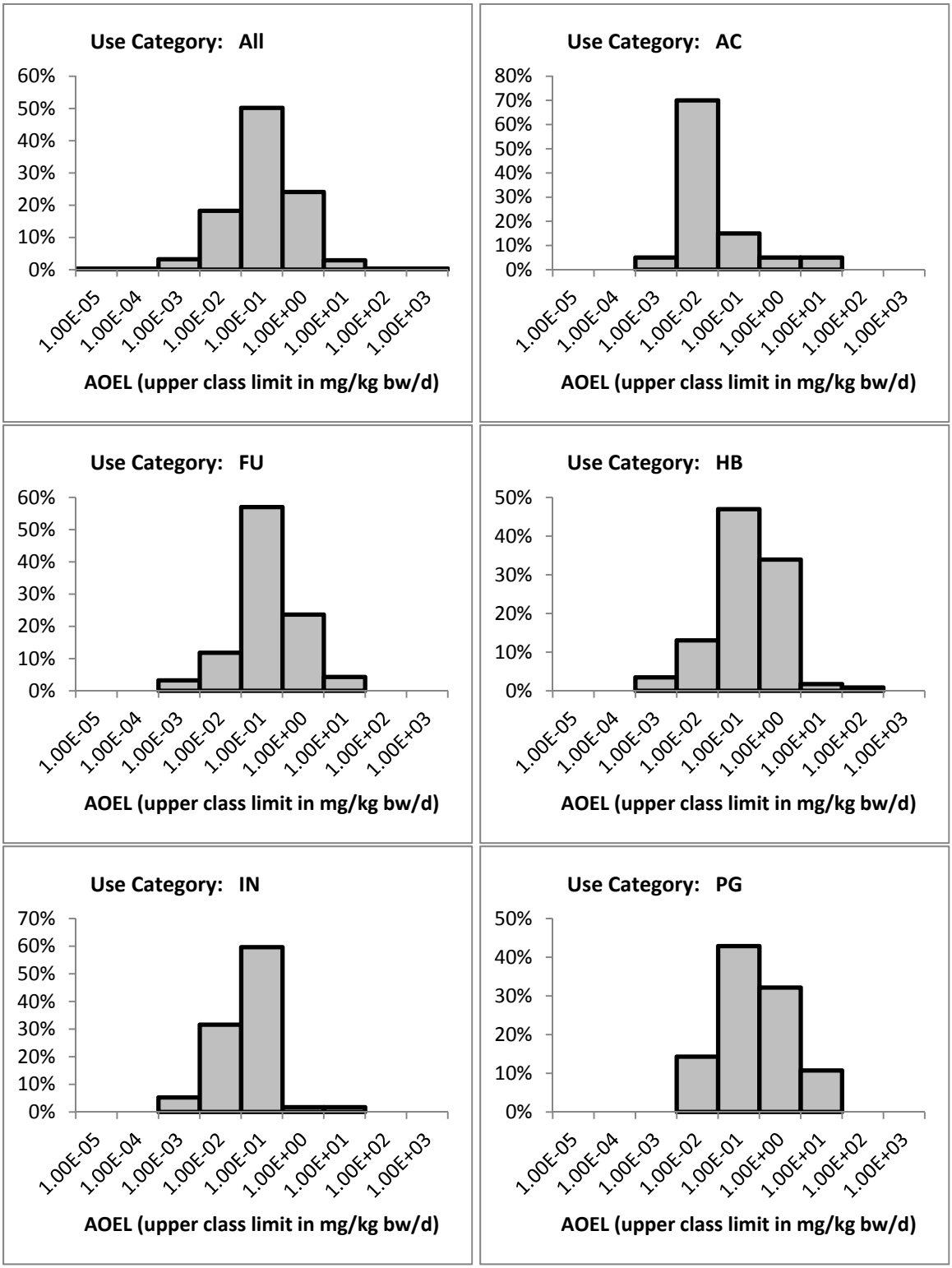


Figure 9 - Histograms of AOEL data



Distribution-dependent thresholds

In the Tables 6 and 7 below, the results of the application of different distribution-dependent thresholds for the identification of CFS are shown for ADI, ARfD, and AOEL values, respectively. Table 6 provides the resulting CFS counts separately for the individual use categories and also separately for the ADI, ARfD, and AOEL criteria. In addition, Table 6 also provides the aggregated counts for all three criteria, ADI, ARfD, and AOEL, but still separated for the different use groups. In Table 7, the data are aggregated across all use groups. The substances that correspond to these counts of CFS are listed in Tables A1, A2, and A3 of the Annex to this report.

The following thresholds were tested:

- "<P1", "<P2", "<P5", "<P10", and "<P20", denote a.s. whose ADI, ARfD or AOEL values are smaller than the 1%, 2%, 5%, 10%, or 20% percentile, respectively.
- "<1SD", and "<2SD" denote substances whose ADI, ARfD or AOEL values are smaller than the arithmetic mean of the log-transformed data minus 1 or 2 times the SD.
- "<0.1 x median", and "<0.01 x median" denote substances whose ADI, ARfD or AOEL values are smaller than $1/10^{th}$ and $1/100^{th}$ of the median value, respectively. As explained above, this measure was applied in order to check whether CFS that are identified by means of statistical distribution parameters are also in a toxicological sense significantly different from the majority of cases.

The three tables A1 to A3 in the Annex to this report include only those of the 378 active substances, which were identified as a CFS by means of one or more of the test criteria applied. Where test criteria result in a positive identification, this is indicated by "YES". Otherwise the value NO or n.a. (not applicable) is given. "Not applicable" here means that the data set was too small for a meaningful application of the respective decision criterion, as explained above.

For part of the substances, different use groups apply simultaneously. For these substances situations occur where the CFS assessment gives inconsistent results for the different use categories. Where this is the case, the use category or categories that drive the identification as a CFS are indicated in brackets after the "YES" in the tables A1 to A3 of the Annex. The results show that the occurrence of such conflicting situations is basically unavoidable if distribution-dependent thresholds are used. A clustering of insecticides and acaricides in a single use group, as is often done, would not be sufficient to eliminate the problem.

The criteria "<1SD", and "<2SD" identify numbers of CFS that are between "<P10", and "<P20", and between "<P2" and "<P5", respectively. This finding is consistent with the assumption that many of the data sets are almost log-normal distributed, which means that 1SD" and "2SD" correspond approximately to 16% and the 2.3% percentiles, respectively.

An important finding is that for all CFS that are identified by the 5% percentile threshold ("<P5"), the ADI, ARfD or AOEL values differ also by more than 1 order of magnitude from the median value ("<0.1 x median"). In contrast, for substances identified by the 10% percentile criterion, the same applies only in a few cases (see tables A1 to A3 of the Annex).

Thus, the 5% percentile appears to be a good discriminator for identifying those active substances that differ significantly from the majority both in statistical as well as in toxicological terms.

A second important observation is that on the level of the 5% percentile, the three criteria ADI, ARfD and AOEL are only weakly correlated. The "<P5" criterion identifies a total of 22 substances. Only 9 of these are double-identified by two of the three criteria simultaneously, the other 13 a.s. are exclusively identified by one of the three criteria.

Table 6 - Number of CFS identified in individual use groups by different statistical measures for low ADI, ARfD and AOEL values

Use Category	Statistical measures as explained in the text								
	<P1	<P2	<P5	<P10	<P20	<1SD	<2SD	<0.1 x median	<0.01 x median
	Low ADI								
AC	*n.a.*	*n.a.*	1	2	4	3	1	0	0
FU	*n.a.*	2	4	8	14	10	2	4	1
HB	2	3	6	12	23	20	3	8	0
IN	*n.a.*	2	2	5	11	9	2	5	0
NE	*n.a.*	*n.a.*	*n.a.*	*n.a.*	2	1	0	0	0
PG	*n.a.*	*n.a.*	1	1	4	4	1	4	0
RE	*n.a.*	*n.a.*	*n.a.*	*n.a.*	1	2	0	2	0
RO	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	1	0	0	0
	Low ARfD								
AC	*n.a.*	*n.a.*	*n.a.*	2	2	4	0	0	0
FU	*n.a.*	1	1	5	11	11	1	1	0
HB	*n.a.*	1	3	5	10	10	1	3	0
IN	*n.a.*	*n.a.*	2	5	10	7	1	2	0
NE	*n.a.*	*n.a.*	*n.a.*	*n.a.*	1	1	0	0	0
PG	*n.a.*	*n.a.*	*n.a.*	2	2	1	0	0	0
RE	*n.a.*	*n.a.*	*n.a.*	*n.a.*	1	1	0	0	0
RO	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	1	0	0	0
	Low AOEL								
AC	*n.a.*	*n.a.*	1	2	4	2	0	0	0
FU	*n.a.*	0	5	10	19	11	3	6	0
HB	1	1	6	11	22	19	4	10	0
IN	*n.a.*	0	3	4	12	10	3	4	0
NE	*n.a.*	*n.a.*	*n.a.*	*n.a.*	1	0	0	0	0
PG	*n.a.*	*n.a.*	0	3	5	5	0	3	0
RE	*n.a.*	*n.a.*	*n.a.*	*n.a.*	1	0	0	0	0
RO	*n.a.*	*n.a.*	*n.a.*	*n.a.*	2	2	0	3	2
	Low ADI and/or low ARfD and/or low AOEL								
AC	*n.a.*	*n.a.*	1	3	5	5	1	0	0
FU	*n.a.*	3	7	15	28	22	4	8	1
HB	2	4	10	19	32	30	7	13	0
IN	*n.a.*	2	6	9	17	13	5	7	0
NE	*n.a.*	*n.a.*	*n.a.*	*n.a.*	3	2	0	0	0
PG	*n.a.*	*n.a.*	1	6	6	6	1	4	0
RE	*n.a.*	*n.a.*	*n.a.*	*n.a.*	3	2	0	2	0
RO	*n.a.*	*n.a.*	*n.a.*	*n.a.*	2	3	0	3	2

Table 7 - Aggregated counts for CFS identified by different statistical measures for low ADI, ARfD and AOEL values

Criterion	Statistical measures as explained in the text								
	<P1	<P2	<P5	<P10	<P20	<1SD	<2SD	<0.1 x median	<0.01 x median
Low ADI	2	7	13	25	51	43	9	21	1
Low ARfD	n.a.	2	6	16	33	32	3	6	0
Low AOEL	1	1	12	27	59	45	8	24	2
Low ADI and/or low ARfD and/or low AOEL	**2**	**9**	**22**	**46**	**85**	**73**	**15**	**35**	**3**

Absolute Thresholds

Distribution-dependent thresholds may have some practical disadvantages:

(i) If two or more different use categories apply to one and the same active substance, conflicting results may occur: the substance may qualify as a CFS for one use category and as a non-CFS for another use category. The practical relevance of this situation has been demonstrated in the preceding section. As a consequence, a use-group-specific CFS identification may be considered as an option in such cases.

(ii) Every change in a data set may change the distribution and consequently the number of active substances identified as a CFS at a relevant point in time. In borderline cases this may mean that an applicant cannot safely predict the outcome of a CFS assessment prior to submission of a dossier.

As a possible alternative option, the setting of absolute threshold values may be discussed. This would eliminate the dynamics of distribution-based thresholds and simplify the procedure. Such an approach could mean that for example a threshold of 0.001 mg/kg is used to discriminate between the majority of ADIs and a minority of very low ADIs in a use group based on the distribution of data observed today. Such an absolute value could be subject to occasional adjustments in the future.

The values could be set differently for different use groups to reflect a uniform proportion of current data sets. For instance, if "<5% percentile" is used as a standard decision criterion as suggested above, this can be transferred into the corresponding absolute value as given for every use group and every criterion in the tables 3 to 5 above.

It may also be considered to simplify the procedure further by applying one and the same absolute value uniformly across different use categories. This could be justified by the argument that the legal text only requires a clear discrimination between the majority and significantly lower values, but not that the affected fraction must be exactly the same for all use groups. In addition, such an approach would have the advantage that toxicologically equivalent decision rules would apply for the identification of CFS across different use groups, thereby eliminating any need for considering use group-specific CFS.

The necessary pre-requisite for a justifiable setting of the same absolute threshold value across different use groups would be that the data distributions for a criterion such as the ADI do not differ very much for the different relevant use groups, so that the affected fraction of

the datasets would be quite similar. The empirical distributions observed (see above) appear to be quite favorable in this respect, at least for a part, but unfortunately not for all the groups.

This is illustrated in the following Tables 8, 9, and 10 for the ADI, ARfD, and AOEL data, respectively. For each of these three criteria, four selected possible decision rules are tested. In case of the ADI (Table 8) these are: ADI<0.001, ≤0.001, ≤0.002, and ≤0.003 mg/kg body weight/day. In this example, a common value might be justifiable for the large groups AC, FU, HB, IN, and PG. Setting the threshold to ADI ≤0.001 mg/kg bw/d for example, would identify between 2% and 9% of the substances in these groups as a CFS.

In contrast, applying the same criterion to the small group of nematicides (NE), which typically have relative low ADI values, would identify half of the substances as being a CFS. This would obviously conflict with the legal requirement for an ADI that is "*significantly lower than those of the majority (…) within groups of substances/use categories*". The opposite situation would occur with the small groups of repellents (RE) and rodenticides (RO), where none of the substances would be affected by this threshold for low ADI values.

Basically, the same situations are observed for ARfD and AOEL data as shown in the Tables 9 and 10. Due to the different data distributions, other absolute values were chosen as test cases, but again a uniform absolute threshold value turns out to be justifiable for the AC, FU, HB, IN, and PG use categories, while for NE, RE, and RO different values would have to be chosen in order to obtain an appropriate discrimination between a minority of relative low values and the majority of significantly higher values.

For three selected possible absolute threshold values the resulting lists of identified CFS are given in the corresponding columns of the tables A1 to A3 in the Annex to this report: ADI ≤ 0.001, ARfD ≤ 0.005, and AOEL ≤ 0.001 mg/kg bw/d. As expectable, the lists differ slightly from those obtained with the "<P5" criterion, with the focus being shifted from small frequencies to low absolute values.

Options provided in the Master Database

As the result of these analyses, the identification of CFS fulfilling Condition 1 by means of a uniform percentile of data appears to be a well justifiable approach, whereby "< 5% percentile" provides a good discriminator for values that are significantly lower than those of the majority, both in statistical as well as in toxicological terms. This approach has therefore been built into the Master Database as a selection tool, whereby the default parameters have been set to "< 5% percentile", and ≥ 20 substances per use group as a minimum requirement for the application of this threshold. However, both parameters can be changed to any other values as needed.

Table 8 - Effect of setting a fixed absolute threshold value for defining low ADI values

Threshold	Unit	Absolute and relative numbers of substances identified as CFS in use groups with ≥ 5 approved active substances								
		AC	FU	HB	IN	NE	PG	RE	RO	ALL
ADI < 0.001 mg/kg bw/d	***no***	**0**	**1**	**3**	**2**	**2**	**1**	**0**	**0**	**8**
	% of quantitative data	0%	1%	3%	4%	29%	4%	0%	0%	3%
	% of all approved a.s.	0%	1%	3%	3%	25%	3%	0%	0%	2%
ADI ≤ 0.001 mg/kg bw/d	***no***	**1**	**2**	**6**	**5**	**4**	**1**	**0**	**0**	**13**
	% of quantitative data	5%	2%	5%	9%	57%	4%	0%	0%	4%
	% of all approved a.s.	4%	2%	5%	7%	50%	3%	0%	0%	3%
ADI ≤ 0.002 mg/kg bw/d	***no***	**1**	**4**	**8**	**5**	**4**	**1**	**0**	**0**	**17**
	% of quantitative data	5%	4%	7%	9%	57%	4%	0%	0%	6%
	% of all approved a.s.	4%	4%	7%	7%	50%	3%	0%	0%	4%
ADI ≤ 0.003 mg/kg bw/d	***no***	**3**	**6**	**12**	**9**	**4**	**4**	**0**	**0**	**30**
	% of quantitative data	15%	7%	10%	16%	57%	16%	0%	0%	10%
	% of all approved a.s.	13%	5%	10%	12%	50%	13%	0%	0%	8%
*Total numbers used as references for calculating percentages**										
Substances with quantitative data		20	91	115	57	7	25	6	4	301
All approved substances		23	114	117	76	8	31	20	8	378

*All percentages rounded to full numbers

Table 9 - Effect of setting a fixed absolute threshold value for defining low ARfD values

Threshold	Unit	Absolute and relative numbers of substances identified as CFS in use groups with ≥ 5 approved active substances								
		AC	FU	HB	IN	NE	PG	RE	RO	ALL
ARfD ≤ 0.003 mg/kg bw/d	***no***	**0**	**0**	**0**	**2**	**2**	**0**	**0**	**0**	**3**
	% of quantitative data	0%	0%	0%	4%	33%	0%	0%	0%	2%
	% of all approved a.s.	0%	0%	0%	3%	25%	0%	0%	0%	1%
ARfD ≤ 0.005 mg/kg bw/d	***no***	**2**	**1**	**1**	**5**	**3**	**0**	**0**	**0**	**9**
	% of quantitative data	13%	2%	2%	10%	50%	0%	0%	0%	5%
	% of all approved a.s.	9%	1%	1%	7%	38%	0%	0%	0%	2%
ARfD ≤ 0.01 mg/kg bw/d	***no***	**4**	**4**	**4**	**10**	**4**	**1**	**0**	**0**	**21**
	% of quantitative data	27%	7%	8%	21%	67%	7%	0%	0%	12%
	% of all approved a.s.	17%	4%	3%	13%	50%	3%	0%	0%	6%
ARfD ≤ 0.02 mg/kg bw/d	***no***	**7**	**9**	**9**	**14**	**4**	**1**	**1**	**0**	**37**
	% of quantitative data	47%	16%	17%	29%	67%	7%	20%	0%	21%
	% of all approved a.s.	30%	8%	8%	18%	50%	3%	5%	0%	10%
*Total numbers used as references for calculating percentages**										
Substances with quantitative data		15	57	52	48	6	14	5	4	178
All approved substances		23	114	117	76	8	31	20	8	378

*All percentages rounded to full numbers

Table 10 - Effect of setting a fixed absolute threshold value for defining low AOEL values

Threshold	Unit	Absolute and relative numbers of substances identified as CFS in use groups with ≥ 5 approved active substances								
		AC	FU	HB	IN	NE	PG	RE	RO	ALL
AOEL < 0.001 mg/kg bw/d	***no***	**0**	**0**	**1**	**0**	**1**	**0**	**0**	**3**	**5**
	% of quanti-tative data	0%	0%	1%	0%	14%	0%	0%	43%	2%
	% of all approved a.s.	0%	0%	1%	0%	13%	0%	0%	38%	1%
AOEL ≤ 0.001 mg/kg bw/d	***no***	**1**	**3**	**4**	**3**	**3**	**0**	**0**	**3**	**12**
	% of quanti-tative data	5%	3%	3%	5%	43%	0%	0%	43%	4%
	% of all approved a.s.	4%	3%	3%	4%	38%	0%	0%	38%	3%
AOEL ≤ 0.002 mg/kg bw/d	***no***	**1**	**3**	**4**	**4**	**3**	**0**	**0**	**3**	**14**
	% of quanti-tative data	5%	3%	3%	7%	43%	0%	0%	43%	5%
	% of all approved a.s.	4%	3%	3%	5%	38%	0%	0%	38%	4%
AOEL ≤ 0.005 mg/kg bw/d	***no***	**6**	**7**	**10**	**11**	**4**	**0**	**0**	**3**	**34**
	% of quanti-tative data	30%	8%	9%	19%	57%	0%	0%	43%	11%
	% of all approved a.s.	26%	6%	9%	14%	50%	0%	0%	38%	9%
*Total numbers used as references for calculating percentages**										
Substances with quantitative data		20	93	115	57	7	28	5	7	307
All approved substances		23	114	117	76	8	31	20	8	378

*All percentages rounded to full numbers

5.4 Background, analysis and results for Condition 2: "*It meets two of the criteria to be considered as a PBT substance*"

Condition 2 indicates that a given a.s shall be approved as CFS if it meets 2 of the criteria to be considered as a PBT substance (i.e. Persistent and Bioaccumulative, Persistent and Toxic or Bioccumulative and Toxic). This criteria has been discussed by an ad-hoc working group set-up by the Commission. Its operationalization is well described in the COM Working Document on "*Evidence needed to identify POP, PBT and vPvB properties for pesticides-Version 3"*. The Commission indicates that the above reference working document has been developed and written specifically to facilitate an understanding of the criteria to be considered for listing an a.s. as CFS.

Section 3.7.2 of Annex II of Regulation (EC) 1107/2009 lists criteria to be considered for the assessment of the persistence, bioaccumulation and toxicity of a given a.s.. It reads as follows:

Box 5.3 - Section 3.7.2. of Annex II of Regulation 1007/2009 (criteria for the approval of an active substance as Persistent, Bioaccumulative, and Toxic

3.7.2. An active substance, safener or synergist shall only be approved if it is not considered to be a persistent, bioaccumulative and toxic (PBT) substance.

A substance that fulfils all three of the criteria of the points below is a PBT substance.

3.7.2.1. Persistence

An active substance, safener or synergist fulfils the persistence criterion where:

- *The half-life in marine water is higher than 60 days,*
- *The half-life in fresh or estuarine water is higher than 40 days,*
- *The half-life in marine sediment is higher than 180 days,*
- *The half-life in fresh or estuarine water sediment is higher than 120 days, or*
- *The half-life in soil is higher than 120 days.*

Assessment of persistency in the environment shall be based on available half-life data collected under appropriate conditions, which shall be described by the applicant.

3.7.2.2. Bioaccumulation

An active substance, safener or synergist fulfils the bioaccumulation criterion where the bioconcentration factor is higher than 2 000.

Assessment of bioaccumulation shall be based on measured data on bioconcentration in aquatic species. Data from both freshwater and marine water species can be used.

3.7.2.3. Toxicity

An active substance, safener or synergist fulfils the toxicity criterion where:

- *The long-term no-observed effect concentration for marine or freshwater organisms is less than 0,01 mg/l,*
- *The substance is classified as carcinogenic (category 1A or 1B), mutagenic (category 1A or 1B), or toxic for reproduction (category 1A, 1B or 2) pursuant to Regulation (EC) No 1272/2008, or*

- *There is other evidence of chronic toxicity, as identified by the classifications STOT RE 1 or STOT RE 2 pursuant to Regulation (EC) No 1272/2008.*

The methodology deployed for each of the 3 criteria: P, B and T is as follows:

Persistence

Article 3.7.2 of Annex II of Regulation (EC) No 1007/2009 lists criteria to be considered for identifying persistent substances in the context of listing CFS and it indicates that assessment of persistency in the environment shall be based on available half-life data collected under appropriate conditions, which shall be described by the applicant.

According to the DG SANCO working document on "*Evidence needed to identify POP, PBT and vPvB properties for pesticides*" – version rev. 3 of 25/09/2012; the assessment shall be based on:

Issue: Persistence assessment - Water/sediment studies - First, the compartment(s) relevant for degradation needs to be established (water, sediment or both). A compartment is relevant for degradation if there is evidence of accumulation in that compartment/partitioning of the substance into that compartment. Then, the cut-off value for that compartment is compared to the whole-system DT50. – *Log KOW values are required to identify the relevant compartment.*

Issue: Persistence assessment - Unextractable residues - Unextractable residues should be excluded from further assessment. They can be considered degradation loss, not bioavailable and therefore unable to exert toxicity.

Issue: PBT /vPvB persistence assessment - Target half-life assessment - half-life should refer to degradation. Data on biodegradation and hydrolysis should be taken into account. Field dissipation studies should be included in the assessment if it is possible to derive degradation half-lives from them, i.e. if it can be excluded that dissipation is due to volatilisation from soil, leaching, surface run-off or uptake into plants. As regards the initial establishment of a list of CFS, photolysis studies should not be considered and field dissipation studies should only be included in the assessment if Vapour pressure $\leq 1 \times 10^{-4}$ Pa at 20°C and Henry's Law constant ≤ 0.1 Pa m^3 mol^{-1}. – *For this reason field studies, vapour pressure and Henry Law values are required for the assessment.*

Issue: Persistence assessment in general - Temperature for normalization of DT50/half-lives - As regards the initial establishment of a list with CFS, all DT50 values should be normalised to a temperature of 20°C. – *For this reason soil temperature values have to be considered during the assessment.*

Issue: PBT /vPvB persistence assessment - Half-lives DT50 - As regards the initial establishment of a list of CFS, if a DT50 value based on single first order kinetics is available in the list of endpoints, the cut-off value should be compared to it directly. Otherwise, the cut-off value should be compared to the DT90 value in the list of endpoints divided by 3.32, provided the DT90 value is calculated and not estimated.

Issue: PBT /vPvB persistence assessment - Appropriate conditions to generate half-lives data - As regards the initial establishment of a list of CFS, anaerobic data should not be considered.

Issue: Persistence assessment in general – Metabolites - As regards CFS, "meeting two of the criteria to be considered as a PBT substance" applies to the active substance but not to its metabolites.

Issue: Persistence assessment in general - Geomean or worst case - As regards the initial establishment of a list of CFS, values from different studies should be aggregated by calculation of the geometric mean. Only DT50 values based on single first order kinetics should be used for data aggregation. When values do not follow first order kinetics, the DT90 value in the list of endpoints should be divided by 3.32 and then included in the calculation of the geometric mean, provided the DT90 value is calculated and not estimated.

Issue: Persistence assessment in general - Stakeholders view on "one compartment approach" - The three PBT criteria referred to in Annex II to Regulation 1107/2009 do not necessarily have to be met in the same compartment.

On the basis of these instructions, the research has focused on the following criteria and corresponding threshold for each individual active substances

- Physico-chemical properties:
    - Vapour pressure ≤1x10-4Pa 20°C (decisive parameter for inclusion of data from field studies)
    - Henry Law constant ≤0.1 Pa m³mol-1
    - Log KOW
- Degradation – laboratory studies:
    - Abiotic – T1/2 hydrolysis DT50
    - Biodegradation (aerobic)
        - T1/2 fresh water >40d
        - T1/2 marine water >60d
        - T1/2 marine sediment >180d
        - T1/2 fresh water/estuarine sediment >120d
        - T1/2 soil>120d
        - soil temperature normalised at 20°C (this normalisation applies to field studies as well)
- Degradation- field dissipation studies (DT50)
    - Abiotic – T1/2 hydrolysis
    - Biodegradation (aerobic)
        - T1/2 fresh water >40d
        - T1/2 marine water >60d
        - T1/2 marine sediment >180d
        - T1/2 fresh water/estuarine sediment >120d
        - T1/2 soil>120d.
        - Soil temperature normalised at 20°C (this normalisation applies to field studies as well)

On the basis of the review of these endpoints and corresponding value(s), the list of persistent active substances has been registered and all evidences qualifying for persistence have been documented in the Excel DB. All the criteria for which a given a.s. is qualifying as CFS are provided.

Figure 10 - Methodological approach to the assessment of persistence

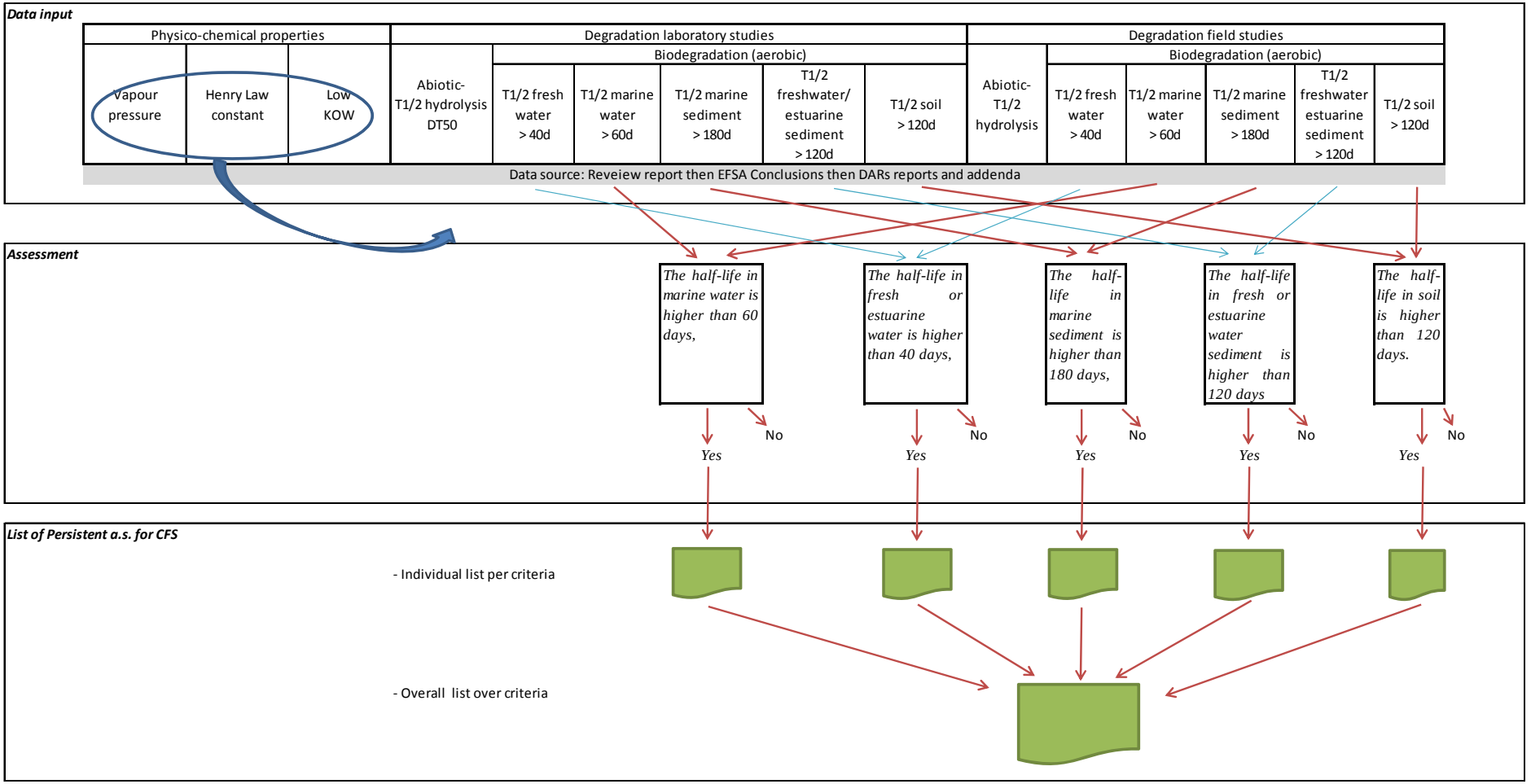


Table 11 - Statistics addressing the identification of persistent a.s.

	No of a.s.
Total number of individual a.s. qualifying as persistent	**121**
of which qualifying as CFS as the half-life in marine water if higher than 60 days	***0***
of which qualifying as CFS as the half-life in fresh or estuarine water is higher than 40 days	***50***
Of which the half-life in marine sediment is higher than 180 days	***0***
Of which the half-life in fresh or estuarine water sediment is higher than 120 days	***76***
Of which the half-life in soil is higher than 120 days (53 a.s. assessed as CFS based on lab data and 30 assessed as CFs based on field data)	***61***

Note: the sum of the number of a.s. in subcategories may be larger than the total number of a.s. given as the total due to the identification of an a.s. by multiple criteria

Bioaccumulation

Concerning bioaccumulation, Article 3.7.2 of Annex II of Regulation (EC) No 1107/2009 stipulates that "*Assessment of bioaccumulation shall be based on measured data on bio concentration in aquatic species. Data from both freshwater and marine water species can be used.*"

Furthermore, point 13 of DG SANCO working document (as referenced above) indicates that "*as regards the initial establishment of a list of CFS, studies in plants should not be included in the assessment*".

The same article further indicates that "*if several studies in animals are available, they should be aggregated:*

a) *In case the studies were performed with the same taxonomic group of organisms (e.g. fish); BCF values should be aggregated by calculation of the geometric mean (as sufficiently similar in design and route exposure);*

b) *In case the studies were performed with different taxonomic groups of organisms, BCF values should be aggregated using the worst case*."

On the basis of these instructions, the analysis consisted in identifying any bio concentration or bioaccumulation factor values in the Commission review reports and in the EFSA conclusions. Only values larger than and equal to 2,000 have been reported in the database. A comment column has been added to the Excel DB to indicate cases that require attention from the Commission and experts.

Figure 11 - Methodological approach to the assessment of bioaccumulative

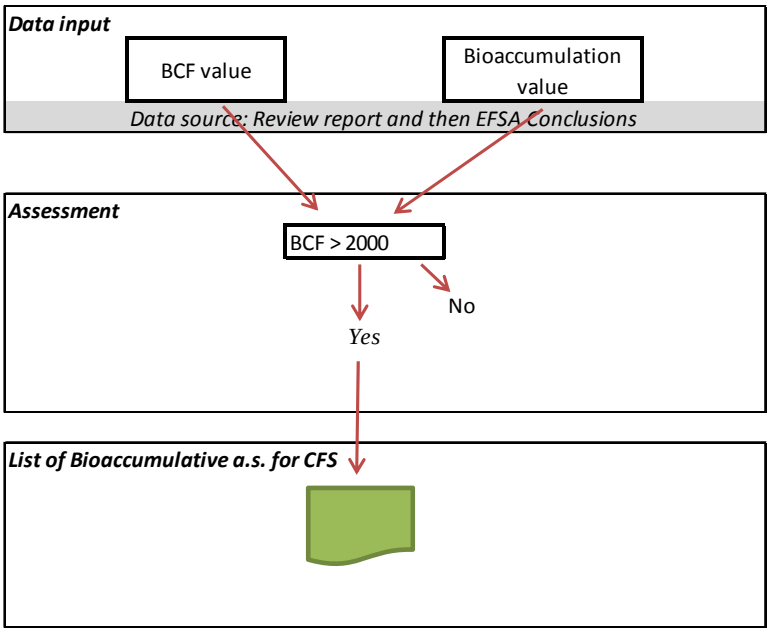


Table 12 - Statistics addressing the identification of bioaccumulative a.s.

	No of a.s.
Total number of individual a.s.qualifying as Bioaccumulative	**17**

Toxicity

Toxicity has to be assessed on three different criteria (see Box 5.3 above). The two last criteria refer to C, M, R and STOT classification pursuant to Regulation (EC) No 1272/2008. This data have been downloaded from the EU pesticides database and the corresponding annexes of Regulation 1278/2008 and entered in the Excel DB for operationalization of the results.

When it relates to the first criteria "*the long-term no-observed effect concentration for marine or freshwater organisms is less than 0.01 mg/l*", the following methodology has been applied.

For each active substance, the Commission review reports and the EFSA conclusions have been screened to identify:

- NOEC and/or EC10 values <0.01 mg/l
- If no NOEC and no EC10, then EC50 values (or equivalent: IC50, LC50) divided by 10 as a surrogate for a NOEC that are < 0.01 mg/l are recorded in the Excel DB.

This analysis considers the two instructions as described in the DG SANCO working document as follows:

- High tier data should not be included in the assessment as exposure might be difficult to standardize;
- When assessing the standard endpoints from algal and aquatic macrophyte studies, the NOEC or EC*x* value should be based on the effect on growth rate.

All identified values qualifying for "*long term NOEC <0.01 mg/l*" have been recorded in the Excel database and for each of the following 4 categories:

- Fish ;
- *Algae ;*
- *Daphnia spp* ; and
- Others.

When NOEC values where not reported nor available, acute toxicity data have been considered for the assessment. All endpoints are reported in the DB. Values for assessing long term toxicity have been extracted from the review reports, the EFSA conclusions and the DARs whenever necessary and other required values from the EU pesticides database (secondary data).

Regarding 'toxicity' the following approach has been discussed and agreed between the contractor and Commission:

- Where for algae there is data on growth rate, only this data should be considered. If there is no such data available, then biomass data is considered acceptable ;
- If no data on the active substance is available, then data on the formulation should be considered ;
- Regarding the chemical form of an active substance (e.g. conjugated forms of the same active substance) no significant differences in data value are expected, and if there is, this should have been reported to the Commission indicating that there is a data reliability issue ;
- All different lots used for testing should be equivalent. Any significant difference should have been reported to Commission ;
- If there is more than one data point available for the same species the lowest value should be used.

Figure 12 - Methodological approach to the assessment of toxicity

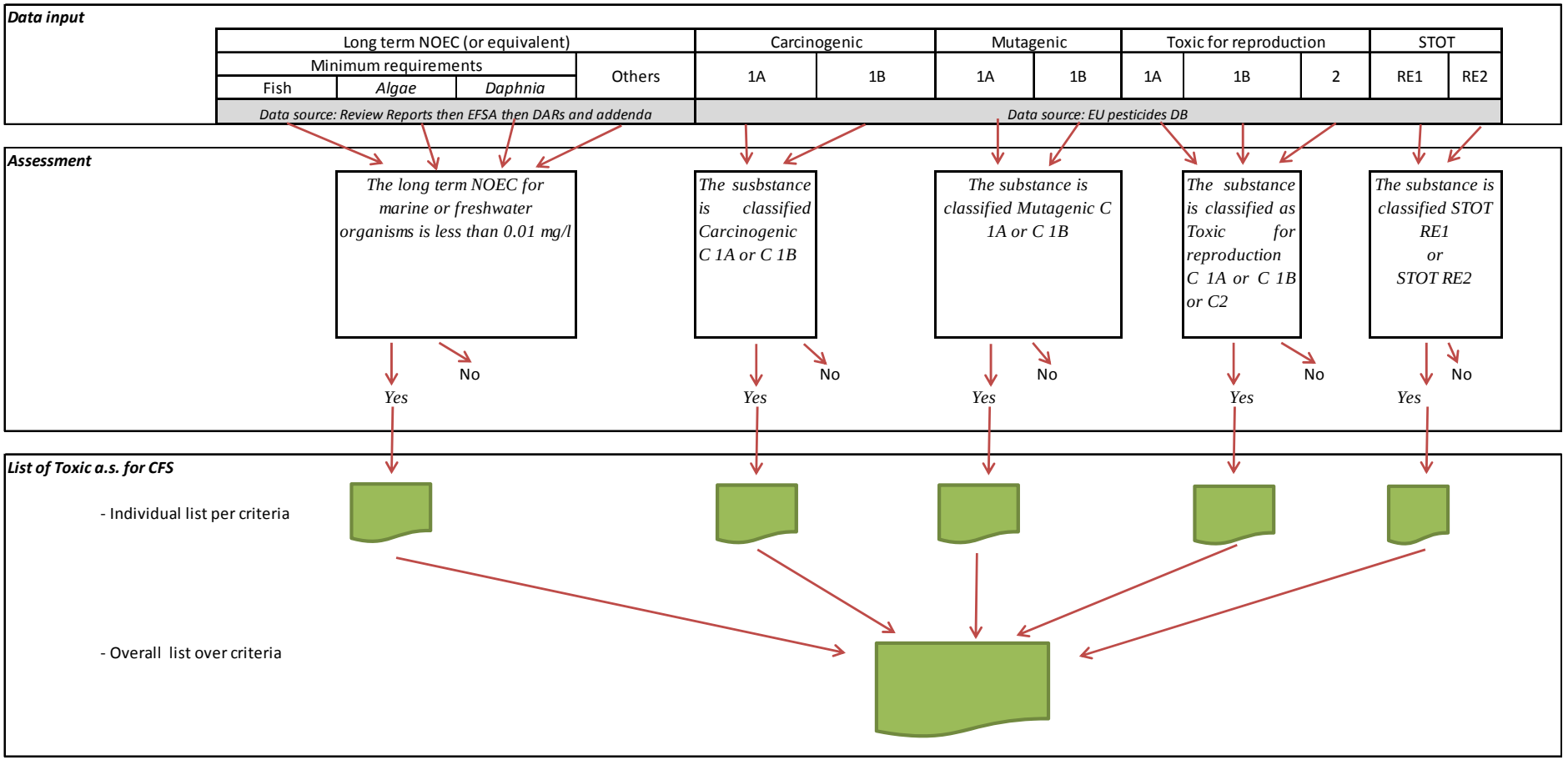


Table 13 - Statistics addressing the identification of toxic a.s.

	No of a.s.
Total number of individual a.s. qualifying as toxic	**189**
of which a.s. qualifying as long term toxic (NOEC<0.01 mg/l)	**173**
of which a.s. qualifying as Carcinogenic 1A or 1B	**0**
of which a.s. qualifying as Mutagenic 1A or 1B	**1**
of which a.s. qualifying as Toxic for reproduction 1A, 1B or 2	**25**
of which a.s. qualifying as STOT RE1 or RE2	**22**

Note: the sum of the number of a.s. in subcategories may be larger than the total number of a.s. given as the total due to the identification of an a.s. by multiple criteria

Conclusions

On the basis of the individual assessment of the persistence, the bioaccumulation and the toxicity, individual a.s. shall qualify as CFS if they meet two or three of these criteria meaning that an a.s. qualifies as CFS if it is P and B, or P and T, or B and T, or P and B and T.

Our analysis leads to the following statistics regarding each of these combinations.

Table 14 - Statistics fulfilling criteria of Condition 2

	No of a.s.
Total number of individual a.s. qualifying as CFS on the basis of criteria of Condition 2	**81**
of which number of a.s. assessed as Persistent and Bioaccumulative	**6**
of which number of a.s. assessed as Persistent and Toxic	**72**
of which number of a.s. assessed as Bioaccumulative and Toxic	**15**
of which number of a.s. assessed as Persistent and Bioaccumulative and Toxic	**6**

Note: the sum of the number of a.s. in subcategories may be larger than the total number of a.s. given as the total due to the identification of an a.s. by multiple criteria

5.5 Background, analysis and results for Condition 3: "*There are reasons for concern linked to the nature of the critical effects (such as developmental neurotoxic or immunotoxic effects) which, in combination with the use/exposure patterns, amount to situations of use that could still cause concern, for example, high potential of risk to groundwater; even with very restrictive risk management measures (such as extensive personal protective equipment or very large buffer zones)*"

In contrast to all other conditions for approving active substances as a CFS, the assessment whether an active substance falls under Condition 3 does not only require information about distinct inherent substance properties, but the integrated consideration of toxicological properties, use conditions and exposure situations is needed.

In the following, options for interpreting the legal text and for substantiating key terms are examined, the availability of relevant information from Review Reports, EFSA Conclusions, and DARs & addenda is checked, and views expressed in other related reports and reviews are taken into consideration. As a result, it is concluded that on the basis of information that is available from Review Reports, EFSA Conclusions, and DARs & addenda, none of the currently approved active substances clearly fulfills Condition 3.

Room for interpretations and proposals for substantiations of terms:

"critical effects"

The term *critical effect* is not defined in Regulation (EC) No 1107/2009, but is used consistently throughout EFSA conclusions. Correspondingly, the term may be interpreted in terms of adverse outcomes that are observed at the lowest effective dose levels, i.e. those that are used to derive an ADI, AOEL, ARfD or other regulatory acceptable levels of exposure.

"reasons for concern linked to the nature of the critical effects"

The term *critical effect* appears twice in Regulation (EC) No 1107/2009. In addition to Condition 3 for CFS identification, it is used with a similar connotation in the context of defining the magnitude of safety margins that shall be used for the establishment of ADI, AOEL and ARfD values (usually 100). In Annex II, under point 3.6.1., it is said: "*When the critical effect is judged of particular significance, such as developmental neurotoxic or immunotoxic effects, an increased margin of safety shall be considered, and applied if necessary.*" As the same examples are given in both passages of the text, the phrases "*reasons for concern linked to the nature*" and "*judged of particular significance*" obviously denote the same type of effects.

Apart from *"developmental neurotoxic or immunotoxic effects",* the text of the Regulation 1107/2009 does not provide further explicit substantiations for critical effects that give *reasons for concern* due to their *nature* or which may be *judged of particular significance.* In addition, substances with other types of effects that are generally associated with high concerns, such as CMRs, PBTs and endocrine disrupters, are explicitly addressed by the other 6 conditions or they cannot be approved under the Regulation.

Given this context and for the purpose of establishing an initial list of CFS on the basis of evidence that is available from Review Reports, EFSA Conclusions, and DARs & addenda, it

is therefore suggested to confine the application of Condition 3 to active substances that exert *"developmental neurotoxic or immunotoxic effects"* as a necessary requirement.

"developmental neurotoxic or immunotoxic effects"

In this phrase it is not totally clear, whether the adjective "*developmental*" applies to *neurotoxic* effects only, or to both, *neurotoxic* and *immunotoxic* effects. So it may be understood to mean either:

(1) Developmental neurotoxic effects or developmental immunotoxic effects, or

(2) Developmental neurotoxic effects or any kind of immunotoxic effects.

In the scientific literature, developmental neurotoxic and developmental immunotoxic effects are discussed as a particular reason for concern because they may mean that the offspring of exposed adults is adversely affected at doses or concentrations that are of no harm to the adults. This may be difficult to detect and may have irreversible long-term effects on populations. In addition, it appears to be inconsistent, if immunotoxic effects are considered to have a particular significance in any case, while neurotoxic effects are judged to be of particular significance only in the offspring and not in the adults.

These considerations argue for option (1) for the interpretation of the phrase. The alternative option (2) could be expected to lead to a larger number of substances fulfilling Condition 3. However, on the basis of the evidence that is currently available for approved substances from Review Reports, EFSA Conclusions, and DARs & addenda this is actually not the case (see below).

Another aspect to be considered here is the fact, that the hazard classification of substances as a reproductive toxicant as defined under Regulation (EC) No 1272/2008 does not only cover adverse effects on sexual function and fertility in adults, but it includes adverse effects on development of the offspring. Developmental neurotoxic or developmental immunotoxic effects are special forms of developmental toxicity. Thus, where substances are known to have developmental neurotoxic or developmental immunotoxic effects, they may be also classified as reproductive toxicants. Depending on the category, this may mean that either they cannot be approved as active substances or they are to be classified as CFS anyway, because Condition 6 is fulfilled.

These considerations may lead to the impression that, apart from providing a double safety-net for developmental neuro- and immuno-toxicants, the main function of Condition 3 could be to provide a clause that may be used in the future in special unforeseeable situations, where new knowledge provides particular reasons for concern relating to yet unknown types of adverse effects that could potentially not be adequately covered by existing assessment schemes.

"in combination with the use/exposure patterns"

This phrase clearly indicates that *developmental neurotoxic or immunotoxic effects,* or other effects judged of similar particular significance, are a necessary but not a sufficient requirement for the fulfillment of Condition 3. Special "*use/exposure patterns"* must apply in addition. Thus, the assessment must not be based on either hazard or exposure considerations alone. There appears to be no room for interpretation of this requirement for a combined assessment.

"use/exposure patterns"

The term *use/exposure patterns* is only used in the definition of Condition 3; it is not used and not defined anywhere else in the text of Regulation (EC) No 1107/2009. However, from the context it seems reasonable to assume that the term is intended to describe any causal or empirical relationship between uses of active substances and their occurrence in environmental media, biota or humans, including metabolites, degradation or reaction products.

Review Reports, EFSA Conclusions, and DARs & addenda can only provide very limited information regarding actual use/exposure patterns, confined to expectations that are based on the evidence generated with one or more representative uses of at least one plant protection product containing the respective active substance. Hence, a full evaluation of all relevant use/exposure patterns that can actually be observed under real use condition would require information that goes far beyond the sources to be considered for the purpose of establishing an initial list of substitution candidates.

"amount to situations of use that could still cause concern"

Approval of active substances is granted under the condition that they have no harmful effect on human health and no unacceptable effect on the environment (Article 4 of Regulation (EC) No 1107/2009). Review Reports, EFSA Conclusions, and DARs & addenda for approved substances should support this conclusion and hence they cannot be expected to provide clear evidence that approved uses *amount to situations (…) that could still cause concern*. This would be a contradiction.

Thus, evidence for *situations of (…) concern* may potentially result from post-marketing experience gained by competent Member States authorities or from related research projects, but the evaluation of such materials was out of the scope of this study.

"high potential of risk to groundwater"

Regulation (EC) No 1107/2009 prescribes that an "*active substance shall only be approved where it has been established for one or more representative uses, that consequently after application of the plant protection product consistent with realistic conditions on use, the predicted concentration of the active substance or of metabolites, degradation or reaction products in groundwater complies with the respective criteria of the uniform principles for evaluation and authorization of plant protection products*" (Annex II, point 3.10). This means that active substances shall not be approved, and the use of plant protection products shall not be authorized, if resulting concentrations in groundwater are expectable to exceed a maximum permissible value of 0.1 µg/l, or a lower limit value where that lower concentration has been laid down in Regulation (EC) No 1107/2009 or where one tenth of the ADI gives a lower value (Annex, Part I, point C.2.5.1.2. of Commission Regulation (EU) No 546/2011 on uniform principles in conjunction with Annex I of Directive 2006/118/EC on the protection of groundwater).

Given these principles, it is self-suggesting to substantiate the phrase "*high potential of risk to groundwater"* in terms of modeled or measured concentrations exceeding the limit value of 0.1 µg/l (or a lower permissible level, where applicable). Where such indications come from monitoring studies, the criterion may be further specified in terms of the magnitude and the frequency of the violations of the limit, taking into account the number of samples and sample sites, as well as trends observed.

As pointed out, expectable compliance with the groundwater quality standard of 0.1 µg/l (or a lower permissible level, where applicable) is an approval criterion. Hence, it cannot be expected that clear evidence for a "*high potential of risk to groundwater"* in terms of an exceedance of the limit value comes from Review Reports, EFSA Conclusions, and DARs & addenda for approved substances. Otherwise the substance might not have been approved. Thus, a full assessment whether a substance has a "*high potential of risk to groundwater"* must draw on the post-marketing evidence generated in Member States monitoring programs.

"risk management measures"

"Risk management measures" is a term that only appears in the definition of Condition 3; it is not used and not defined anywhere else in the text of Regulation (EC) No 1107/2009.

However, Article 6 says that the approval of active substances may be subject to "*conditions and restrictions*", *inter alia* including the manner and conditions of application, the designation of areas where the use of plant protection products containing the active substance may not be authorized, or the need to impose risk mitigation measures and monitoring after use. Correspondingly, the uniform principles for evaluation and authorization of plant protection products laid down in Commission Regulation (EU) No 546/2011 prescribe that Member States shall impose "*conditions and restrictions*" with the authorisations they grant, where appropriate. "*The nature and severity of these measures must be selected on the basis of, and be appropriate to, the nature and extent of the expected advantages and the risks likely to arise* (Annex, Part I, section C.1.).

Given this context, it appears reasonable to assume that the term "*risk management measures"* is meant as a collective denotation of "*conditions and restrictions*" imposed with both the approval of active substances and the authorisation of corresponding plant protection products with the aim to ensure their safe use.

This implies that only part of the relevant information is available from Review Reports, EFSA Conclusions, and DARs & addenda. A full assessment whether Condition 3 applies to a given active substance would require considerations of the conditions and restrictions that Member States actually impose on plant protection products containing that substance.

"very restrictive risk management measures (such as extensive personal protective equipment or very large buffer zones)"

Condition 3 requires a distinction to be made between very restrictive risk management measures and less restrictive measures. As the examples of personal protective equipment and buffer zones show, risk management may comprise a variety of very different types of measures. Therefore, a uniform scale for quantifying the degree of restrictiveness seems hardly definable. Theoretically, it should indeed be possible to express and to compare the degree of restrictiveness of all measures in monetary terms; practically however, this requires detailed economic analyses that usually are not available. Thus, for the practical assessment of Condition 3, a simpler qualitative approach to the substantiation of the term "*very restrictive*" is necessary.

Semantically, "*very restrictive*" may be taken to denote a situation, where the measures can hardly be strengthened any more, may be for mere technical reasons, or because the use of the active substance in plant protection products would become practically and/or economically unfeasible. Generally speaking, this means that risk management measures are "*very restrictive"*, if the only remaining option for improved achievement of the protection goals is

to abandon the use of the active substance for the relevant purpose and to replace it by other substances or measures.

Further specifications of this general interpretation could be derived for specific types of substance uses and for specific types of risk mitigation measures. However, this requires information about actual use conditions and risk mitigation measures taken on the Member States level, knowledge that is not available from Review Reports, EFSA Conclusions, and DARs & addenda.

"buffer zones"

The term *buffer zones* is only used in the definition of Condition 3; it is not used and not defined anywhere else in the text of Regulation (EC) No 1107/2009. The term is usually used to denote minimum distances between spray applications of PPPs and watercourses, prescribed by regulatory authorities for the purpose of protecting aquatic life. This is not directly related to preventing risk to groundwater or with protecting humans from developmental toxic effects. Thus, it may be assumed, that the term is used here just as another illustration for the term *risk management measures,* and with no particular connotation to other key terms of the sentence. However, in English speaking countries, the term *buffer zones* is sometimes also colloquially used for distances between fields sprayed with pesticides and the homes of adjacent residents. May be, this was meant here.

However, as with other *risk management measures,* an assessment whether the *buffer zones* are "*very large"* and hence "*very restrictive*" would require information that is not available from Review Reports, EFSA Conclusions, and DARs & addenda. Hence, a final interpretation of the term was not critical for this study.

Available Information from relevant sources (Review reports, EFSA Conclusions and DARs and addenda)

Developmental neurotoxic effects

All available EFSA conclusions and review reports (772 documents) were searched for the terms "developmental neurotoxic" and "developmental neurotoxicity". Hits were found in 3 and 42 documents, respectively. These documents related to a total of 37 different active substances.

Checking of the documents gave the following picture:

- For 14 substances the hits resulted from statements about non-available data ;
- For 13 substances negative findings were reported or effects were observed at maternal toxic doses only ;
- For 7 substances effects were seen in animal studies, but they were not critical for deriving an ADI, AOEL, or ARfD (other effects were seen at lower doses) ;
- For 3 substances developmental neurotoxic effects were critical for setting the AOEL (dimethoate) or the ARfD (fipronil and mepiquat).

For all three developmental neuro-toxicants, dimethoate, fipronil and mepiquat, specific provisions are laid down in the list of approved active substances (Regulation (EU) No 540/2011), asking Member States to pay particular attention to specific aspects of human

and/or environmental health, when authorizing plant protection products containing these substances. Whether in practice, this leads to a sufficient level of protection, or whether there are *use/exposure patterns* that in combination with the critical developmental neurotoxic properties *amount to situations of use that could still cause concern* cannot be finally answered on the basis of the information sources examined in this study.

Immunotoxic effects

Searches for the terms "*developmental immunotox*" and "*developmental immunotoxicity*" in all available Review Reports and EFSA conclusions gave no hits.

Searches for "*immunotoxic*", "*immunotoxicity*", and "*immunotoxicological*" (without the confinement to developmental immunotoxicity) give hits in documents for a total of 11 substances. Closer examination of the information in these documents revealed that in all cases, either no immunotoxicity was observed or only indirect effects were observed or the effects were not critical for the derivation of acceptable levels because other effects were seen at lower doses.

Thus, on the basis of information available from Review Reports and EFSA Conclusions, the immunotoxicity criterion does not lead to the identification of any substances that could potentially fall under Condition 3, regardless whether general immunotoxicity is taken into consideration or developmental immunotoxicity only.

5.6 Background, analysis and results for Condition 4: "*It contains a significant proportion of non-active isomers*"

Isomers are chemical compounds with the same molecular formula but different structural formulas. Pesticide-inactive isomers that are present in an approved active substance may be toxic to humans or non-target organisms in the environment and they may have different fate and degradation characteristics (Magrans, Alonso-Prados and García-Baudin 2002, Wong 2006) [19,20]. Therefore they require consideration within the approval procedure.

Regulation (EU) No 544/2011 on information requirements for active substances states that "*the maximum content in g/kg of inactive isomers (…) must be provided*" (Annex, Part A, point 1.10.). However, as detailed below, extensive searches in the information sources that are relevant for this study have shown that such information is difficult to find for the vast majority of active substances that were on the list of approved substances at the relevant record date (31 January 2013).

The only exemptions from this finding are compounds that have been approved both as an isomer mix and as a single active isomer. In these cases, the isomer mix may be considered as a CFS, as detailed below.

On the basis of information that is available from Review Reports, EFSA Conclusions, and DARs & addenda, this situation currently applies to two pairs of approved active substances: mecoprop and mecoprop-P, as well as metalaxyl and metalaxyl-M. Hence, the racemic isomer mixes mecoprop and metalyxyl may be considered as CFS fulfilling Condition 4.

Implications of Condition 4

The formulation of Condition 4 implies that three requirements must be fulfilled for the identification of a corresponding CFS:

(1) The active substance must be known to be a **mixture of isomers** ;

(2) One or more of these isomers must be known to be **non-active** against target organism ; and

(3) The amount of this or these non-active isomer(s) must be assessed to make up a **significant proportion** of the total active substance.

In the following, these three requirements are consecutively considered in terms of both data availability from relevant sources and options for interpretation and substantiation of key phrases.

Searching for approved substances that are mixtures of isomers

Condition 4 is not applicable to approved active substances that are micro-organisms, but to chemicals only. By inspection of the substance names, 29 of the 378 relevant approved

[19] Magrans JO, Alonso-Prados JL, García-Baudin JM (2002) Importance of considering pesticide stereoisomerism – proposal of a scheme to apply Directive 91/414/EEC framework to pesticide active substances manufactured as isomeric mixtures. Chemosphere 49, 461-469

[20] Wong CS (2006) Environmental fate processes and biochemical transformations of chiral emerging organic pollutants. Anal Bioanal Chem 386, 544-558

substances were identified as viruses or bacteria. They are excluded from all further considerations.

As a second pre-requisite, Condition 4 implies that the chemicals of concern must be well defined in terms of their molecular structure. An assessment of Condition 4 is not applicable to substances that are complex mixtures of not fully known compounds with variable composition, such as oils, fats, plant extracts or blood meal for instance. As a consequence, all chemical substances that are not defined by a systematic chemical name according the IUPAC nomenclature of chemistry were out of the scope of all further considerations. This criterion excluded another set of 25 substances.

Basically, two main types of isomers have to be distinguished: structural isomers, also called constitutional isomers, and stereoisomers, sometimes also referred to as spatial isomers. In structural isomers, atoms have a different connectivity, i.e. they are bonded to each other in a different way. In stereoisomers, in contrast, atoms have the same connectivity, only their orientation in space differs. Structural isomers are different compounds with different physico-chemical properties and they are denoted by different IUPAC names. A check of the IUPAC names of the remaining 324 relevant substances revealed that none of them is a mix of structural isomers. Hence, all further considerations are confined to stereoisomerism.

For identifying approved substances that are mixes of stereoisomers on the basis of the information sources that are relevant for this study, two complementary approaches were taken: (i) all IUPAC names were checked for stereo-descriptors, and (ii) all EFSA Conclusions and Review Reports were searched for the term “isomer” and the corresponding text passages were examined for relevant information.

According to the principles of the IUPAC nomenclature of organic chemistry, the spatial structure of an organic compound is systematically indicated by one or more affixes, such as (+)/(-), R/S, E/Z, D/L, or cis/trans). These affixes are added to a name that does not itself prescribe the stereo-chemical configuration of a molecule and they are generally called stereo-descriptors. Where such stereo-descriptors were detected in a IUPAC name, it was checked whether they specify the molecule as a single isomer or as an isomer mix. The resulting list was counter-checked with the additional textual information identified by the keyword search and corrected or amended where necessary.

As a result of this exercise:

- 71 approved substances were identified as a mix of stereoisomers (Table 15),
- 49 approved substances were found to be single isomers (or mixtures of single isomers of different compounds),
- For 204 approved substances no indications for the existence of different stereoisomers were obtained by this approach.

From the 204 substances with no positive indications on isomerism, 16 are types of inorganic molecules for which in fact certainly no isomers exist. For the remaining 188 organic substances, a final confirmation would require to consult other information sources than those relevant for this study.

However, Regulation (EU) No 544/2011 on information requirements for active substances prescribes that "*the structural formula of each stereo and optical isomer present in the active substance must be provided*" (Annex, Part A, point 1.7.).

This gives a reason to assume that where such information is totally missing in the EFSA conclusions, the probability that the substance is in fact an isomer mix should not be very high.

Table 15 - Approved active substances that are unresolved mixtures of stereo-isomers

Alpha-Cypermethrin	Difenacoum	Hexythiazox	Propiconazole
Beflubutamid	Difenoconazole	Imazalil	Prothioconazole
Benalaxyl	Dimethomorph	Imazamox	Pyriproxyfen
Beta-Cyfluthrin	Dodemorph	Imazaquin	S-Metolachlor
Bifenthrin	Epoxiconazole	Iprovalicarb	Spiroxamine
Bitertanol	Ethofumesate	Isopyrazam	tau-Fluvalinate
Bromadiolone	Etoxazole	lambda-Cyhalothrin	Tebuconazole
Bromuconazole	Fenamiphos	Lufenuron	Tefluthrin
Carfentrazone-ethyl	Fenbuconazole	Malathion	Tepraloxydim
Carvone	Fenpropidin	Mecoprop	Tetraconazole
Clethodim	Fenpropimorph	Metalaxyl	Thiamethoxam
Cycloxydim	Fipronil	Metaldehyde	Tralkoxydim
Cyflumetofen	Flurochloridone	Metconazole	Triadimenol
Cyfluthrin	Fluroxypyr*	Myclobutanil	Triticonazole
Cymoxanil	Flurtamone	Napropamide	Warfarin
Cypermethrin	Flutriafol	Paclobutrazol	zeta-Cypermethrin
Cyproconazole	Fosthiazate	Penconazole	Zoxamide
Diclofop	Glufosinate	Profoxydim	

* meptyl ester variant only

Searching for non-active isomers

For all the 71 identified mixes of stereoisomers, EFSA Conclusions and/or Review Reports were carefully searched for any relevant statement about active, inactive or non-active isomers or any other explicit or implicit information about different activities of the isomers against target organisms. The results were totally negative in all but just one case: mecoprop.

In the Review Report for the active substance mecoprop (SANCO/3063/99-Final 14 April 2003), the following bit of information was spotted in Appendix II, section 3 on Ecotoxicology: *"…studies are performed with different active ingredients (…): Mecoprop, the "true" active ingredient, the raceme, (…) Mecoprop-P, the active isomer"*. This was the only hint in the Commission document that points to the well-known fact that mecoprop is a racemic mixture of a herbicidally active and a herbicidally inactive isomer, while mecoprop-P is enriched in the active isomer form (US EPA 2007) [21].

The mecoprop case shows that the co-existence of both an unresolved isomer mixture and an individual active isomer on the pesticide market can provide an indirect indication for one or more inactive isomers being contained in the mixture. As a consequence, we also checked for all other 70 mixtures of isomers, whether any of the corresponding single isomers were also

[21] US EPA (United States Environmental Protection Agency) (2007) Reregistration Eligibility Decision (RED) for Mecoprop-p (mcpp). Available at http://www.epa.gov/oppsrrd1/REDs/mcpp_red.pdf; accessed 31.05.2013.

on the list of approved active substances at the relevant record date (31 January 2013). As a result, a further pair of active substances was detected: the unresolved mixture metalaxyl and the corresponding enriched single isomer metalaxyl-M.

No explicit information about the differences in the activities of the isomers against target organisms was found in the Review Reports for the active substances metalaxyl (SANCO/10476/2010 – rev.1 12 March 2010) and metalaxyl-M (SANCO/3037/99-final 18 September 2002). However, also in this case, it is well known that metalaxyl is a racemic mixture of a fungicidally active and a fungicidally inactive isomer, while metalaxyl-M is enriched in the active isomer form (e.g. WHO/FAO 2005).

Significance of the proportion

According to the available pieces of information outlined above, both mecoprop and metalaxyl are racemic mixtures, which means that they contain the active and the inactive isomer forms in equal amounts. Hence 50% of the approved active substance have no benefits but may pose known or unknown risks to human health and the environment. As this is the highest possible proportion, it may be considered as being significant in any case, although specific toxicological or ecotoxicological assessments of the inactive isomers were not available from the relevant information sources.

5.7 Background, analysis and results for Condition 5, Condition 6 and Condition 7.

Condition 5, Condition 6 and Condition 7 are based on the present and future Classification, Labelling and Packaging (CLP)[22] classification as follows:

- Condition 5: "*It is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogen 1A or 1B if the substance has not been excluded in accordance with the criteria laid down in point 3.6.3 [of Regulation 1107/2009]*" ;
- Condition 6: "*It is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 1A or 1B if the substance has not been excluded in accordance with the criteria laid down in point 3.6.4 [of Regulation 1107/2009]*" ;
- Condition 7: "*If, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, reviewed by the Authority, it is considered to have endocrine disrupting properties that may cause adverse effects in humans if the substance has not been excluded in accordance with the criteria laid down in point 3.6.5 [of Regulation 1107/2009]".* As specified in the ToR of the study, pending the adoption of criteria on endocrine disrupting properties, substances that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogenic category 2 AND toxic for reproduction category 2, shall be considered to have endocrine disrupting properties.

Annex II (4) stipulates that an a.s. should be listed as CFS if "*they are*" OR "*are to be classified*" as carcinogenic or toxic for reproduction in Regulation (EC) No 1272/2008. When information related to the actual classification is easily available in Table 3.1 of Annex V of the above mentioned Regulation 1272/2008, the future possible classification of PPP a.s. needs to be investigated.

These criteria leave no room for interpretation. However, approval under Regulation 1107/2009 and classification under the CLP Regulation 1272/2008 are not fully synchronized processes.

With respect to endocrine disrupting properties where the interim criteria shall apply for the purpose of this study (C2 AND R2), there is also no room for interpretation. The problem of different timing of PPP and CLP decisions is the same as for C1 and R1.

The PPP Regulation (EC) No 1107/2009 was published on 24 November 2009 and entered into force 20 days later. Regarding classification of hazardous substances, this was done during a transition period from the old classification system under Directive 67/548/EEC to the new (globally) Harmonised Classification & Labelling (CLH) under the CLP Regulation (EC) No 1272/2008.

Until 10 December 2010, the old classifications under Directive 67/548/EEC continued to apply to single substances (Regulation 1272/2008, Art 61) (and for mixtures they still

[22] On 20 January 2009 the Regulation (EC) No 1272 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 entered into force. It aligns existing EU legislation to the United Nations Globally Harmonised System (GHS).

continue to apply until 2015). This means, that, at the time of publication of the new Regulation 1107/2009, any substance that was classified as a class 1 or 2 carcinogen under the old system, was considered to be a substance "*that is to be classified, in accordance with ... 1272/2008, as a carcinogen category 1A or 1B*". Corresponding considerations apply to reprotoxic substances.

ECHA and EFSA try to streamline their assessments of hazardous properties under the CLP and the PPP Regulation 1107/2009, respectively[23] . However, formally these are separate procedures. The Commission takes a decision on approval or non-approval of an active substance under the PPP Regulation 1107/2009 and under consideration of the corresponding DAR and EFSA conclusions only, without a formal requirement for the simultaneous existence of an agreed definitive classification under CLP Regulation 1272/2008. Thus in principle and during interim phases, situations where a Commission decision is based on a classification proposed by EFSA while a corresponding classification by ECHA under Regulation 1272/2008 has not yet been established cannot be excluded.

The ECHA website provides several sources from which information on current and possible future classification according to the provisions of the CLP Regulation (EC) 1272/2008 can be retrieved.

Nevertheless, some of these substances might be registered by the end of May 2013 (registration deadline for substances which are placed on the EU market in a volume between 100 - 1,000 tons/year). In order to cross-check these substances, a PDF-document or an Excel-sheet is available via a link[24] and includes those substances which are intended to be registered (according to provided intentions of companies) by this deadline. If no entries in Annex VI to the CLP Regulation 1272/2008 are available, then the documents elaborated in the procedural steps towards classification can be used as source for checking the planned classification of a substance.

Before a substance is included in Part 3 of Annex VI to the CLP Regulation 1272/2008, several hurdles have to be negotiated.

The overall procedure for a harmonised classification and labelling can be outlined as follows (the following text has been extracted from a document published by ECHA)[25]:

1. Maintaining the Registry of Intentions (RoI): The RoI is updated when a notification of intention to prepare a CLH dossier is received, when a CLH dossier is submitted or when an intention/submission is withdrawn.

2. Dossier reception and accordance check: The dossier is stored and checked for accordance with regard to the legal requirements of the CLP Regulation and with the recommendations provided in the Guidance for the preparation of a CLH dossier. The dossier submitter (DS) is informed about the outcome of the accordance check. When the CLH dossier fails the accordance check, the DS may decide to resubmit it. The

[23] Roland Solecki, Abdelkarim Abdellaue, Teresa Borges, Kaija Kallio-Mannila, Herbert Köpp, Thierry Mercier, Vera Ritz, Gabriele Schöning and José Tarazona: Report of the Workshop on Harmonized Classification and Labelling (CLH) of Active Substances in Plant Protection Products held in Berlin on 12 and 13 April 2011.

[24] http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances/identified-substances-for-registration-in-2013

[25] http://echa.europa.eu/documents/10162/13607/procedure_harmonisation_classification_labelling_en.pdf

public consultation is launched for CLH dossiers which are in accordance with legal requirements.

3. Developing the RAC opinion: The comments received on the CLH proposal during the public consultation are compiled in a Response to Comments (RCOM) document and sent to the DS. The DS responds to the comments in the RCOM and submits it to ECHA. ECHA forwards the RCOM and the CLH report to RAC. RAC assesses the CLH report and RCOM document and prepares an opinion on the proposed classification and labelling.

4. Adoption of the RAC opinion: The opinion is adopted either in a RAC plenary meeting or through a written discussion and sent to the European Commission. At the same time, the documents are published on the ECHA website. Each CLH dossier is processed by a CLH team (CLH_T) consisting of staff of the Classification Unit and the Committees Secretariat Unit, as well as other units, when appropriate. One team may have the responsibility for multiple dossiers. The CLH_T provides scientific, technical and administrative support to the RAC Chair and to the Rapporteurs of the Committee for Risk Assessment (RAP). This support includes the sound and timely management and the correct procedural records of the work of the ECHA Secretariat and of RAC.

For each of the aforementioned steps ECHA regularly publishes information on ongoing activities and the current status on its website.

In this context the RAC scientific opinions on harmonised Classification and Labelling represent the closest stage to a final classification by the European Commission and a consensual opinion of expert representatives from all Member States. Therefore the investigations on "to be classified" in the mentioned Excel sheet refer to the elaborated RAC´s opinions where such were available. After approval of the European Commission classifications are included in subsequent ATPs (Adaptation to Technical and scientific Progress) amending the CLP Regulation[26] and which are updated and published in regular terms.

What ECHA has done to review/complete the 1272/2008 classification since its entry into force?
Regulation (EC) No 1272/2008 of the European Parliament and of the Council entered into force on 16 December 2008. ECHA has submitted several proposals for harmonised Classification and Labelling. Since entering into force several amendments have been adopted.

On the basis of the review of these different considerations, the database has been completed with data marked as "*to be classified*". An additional sheet has been added to the Excel database to demonstrate the rationale of the classification (see sheet: R&C to be classified).

[26] http://echa.europa.eu/web/guest/regulations/clp/legislation

Table 16 - Statistics regarding CFS qualification based on conditions 5, 6 and 7

CFS criterion	Number of a.s.
Condition 5	**0**
of which classified as Carc. 1A	**0**
of which classified as Carc. 1B	**0**
of which to be classified Carc. 1A	**0**
of which to be classified Carc. 1B	**0**
Condition 6	**9**
of which classified as Toxic for repr. 1A	**2**
of which classified as Toxic for repr. 1B	**6**
of which to be classified as Toxic for repr. 1A	**0**
of which to be classified as Toxic for repr. 1B	**1**
Condition 7	**7**
of which classified as Carc.2	**22**
of which classified as Toxic for repr. 2	**17**
of which to be classified as Carc.2	**13**
of which to be classified as Toxic for repr. 2	**10**
of which classified as Carc.2 and Toxic for repr. 2	**6**
of which to be classified as Carc.2 and Toxic for repr. 2	**1**

5.8 Summary of results

The analysis has been carried out considering the approved active substances until January 2013, as structured in the Annex of Regulation (EU) 540/2011 leading to a total of 378 under consideration.

Depending on the chosen options a total of around 100 actives substances could be defined as CFS as they conform to, at least, one of the seven conditions in Annex II, chapter 4 of the Regulation (EC) No 1107/2009.

The conditions which define each active substance as CFS are clearly presented in the Excel database. They are summarised as follows:

Condition 1: Its ADI, ARfD or AOEL is significantly lower than those of the majority of the approved active substances within groups of substances/use categories

This condition may be defined in statistical terms (fractions of the median, multiples of the SD from the mean, and percentiles of a ranked data set) or toxicological terms (fixed absolute thresholds). Depending on the chosen option the number of substances that fulfil condition 1 varies.
The 5% percentile appears to be a good discriminator for identifying those active substances that differ significantly from the majority both in statistical as well as in toxicological terms. On the basis of this approach 22 active substances qualify for this condition of which 13 for low ADI value, 6 for low ARfD value and 12 for low AOEL value.

Condition 2: It meets two of the criteria to be considered as a PBT substance

Eighty-one (81) active substances fulfil 2 PBTs condition (121 active substances have been assessed as being persistent, 17 as being bioaccumulative and 89 as being toxic). For individual substances all evidences for the qualification are reported in the DMS.

Condition 3: There are reasons for concern linked to the nature of the critical effects (such as developmental neurotoxic or immunotoxic effects) which, in combination with the use/exposure patterns, amount to situations of use that could still cause concern, for example, high potential of risk to groundwater; even with very restrictive risk management measures (such as extensive personal protective equipment or very large buffer zones)

In contrast to all other conditions for approving active substances as a CFS, the assessment whether an active substance falls under Condition 3 does not only require information about distinct inherent substance properties, but the integrated consideration of toxicological properties, use conditions and exposure situations is needed. As a result of the research, it is concluded that none of the currently approved active substances clearly fulfills Condition 3 as no agreed data have been identified for the qualification as CFS.

Condition 4: It contains a significant proportion of non-active isomers

On the basis of information that is available from Review Reports, EFSA Conclusions, and DARs & addenda, the racemic isomer mixes of 2 substances may be considered as CFS.

Condition 5: It is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogen category 1A or 1B, if the substance has not been excluded in accordance with the criteria laid down in point 3.6.3 of Annex II of Regulation (EC) No 1107/2009

No active substance qualifies for CFS based on Condition 5.

Condition 6: It is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 1A or 1B if the substance has not been excluded in accordance with the criteria laid down in point 3.6.4 of Regulation (EC) No 1107/2009

Nine (9) active substances are classified or are to be classified as toxic for reproduction.

Condition 7: If, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, reviewed by the Authority, it is considered to have endocrine disrupting properties that may cause adverse effects in humans if the substance has not been excluded in accordance with the criteria laid down in point 3.6.5 of Regulation (EC) No 1107/2009

The research identified 7 active substances that may be classified as CFS depending upon the application of the temporary provisions for potential endocrine disruptors.

Individual listing of active substances qualifying for CFS conditions and sub-criteria are presented in annexes.

ANNEXES

Table A 1 - Identification of CFS by low ADI values

Active Substance	Use Category	Different optional definitions of "low" as explained in the legend									
		<P1	<P2	<P5	<P10	<P20	<1SD	<2SD	<0.1 x median	<0.01 x median	≤0.001 mg/kg/d
Fluometuron	HB	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES
Sulcotrione	HB	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES
Triazoxide	FU	*n.a.*	YES	YES	YES	YES	YES	YES	YES	YES	YES
Ethoprophos	NE, IN	*n.a.*	YES (IN)	YES (IN)	YES (IN)	YES	YES	YES (IN)	YES (IN)	NO	YES*
Metam (incl. -potassium and -sodium)	FU, IN, HB, NE	NO	YES (FU)	YES (FU, HB)	YES (FU, HB, IN)	YES (FU, HB, IN)	YES (FU, HB, IN)	YES (FU)	YES (FU, HB, IN)	NO	YES*
Haloxyfop-P (Haloxyfop-R)	HB	NO	YES	YES	YES	YES	YES	YES	YES	NO	YES
Fipronil	IN	*n.a.*	YES	YES	YES	YES	YES	YES	YES	NO	YES
Dimethoate	IN, AC	*n.a.*	NO	YES (AC)	YES	YES	YES	YES (AC)	YES (IN)	NO	YES
1-Methylcyclopropene	PG	*n.a.*	*n.a.*	YES	YES	YES	YES	YES	YES	NO	YES
Amitrole (aminotriazole)	HB	NO	NO	YES	YES	YES	YES	NO	YES	NO	YES
Diclofop	HB	NO	NO	YES	YES	YES	YES	NO	YES	NO	YES
Fluquinconazole	FU	*n.a.*	NO	YES	YES	YES	YES	NO	YES	NO	
Flusilazole	FU	*n.a.*	NO	YES	YES	YES	YES	NO	YES	NO	
Oxamyl	IN, NE	*n.a.*	NO	NO	YES (IN)	YES (IN)	YES (IN)	NO	YES (IN)	NO	YES*
Diquat (dibromide)	HB, DE	NO	NO	NO	YES (HB)	YES (HB)	YES (HB)	NO	YES (HB)	NO	
Quinoclamine	AL,HB	NO	NO	NO	YES (HB)	YES (HB)	YES (HB)	NO	YES (HB)	NO	
Abamectin (aka avermectin)	AC, IN	*n.a.*	NO	NO	YES (AC)	YES	YES	NO	NO	NO	
Clodinafop	HB	NO	NO	NO	YES	YES	YES	NO	NO	NO	
Cyhalofop-butyl	HB	NO	NO	NO	YES	YES	YES	NO	NO	NO	
Linuron	HB	NO	NO	NO	YES	YES	YES	NO	NO	NO	
Oxyfluorfen	HB	NO	NO	NO	YES	YES	YES	NO	NO	NO	
Bitertanol	FU	*n.a.*	NO	NO	YES	YES	YES	NO	NO	NO	
Dimoxystrobin	FU	*n.a.*	NO	NO	YES	YES	YES	NO	NO	NO	
Fenpropimorph	FU	*n.a.*	NO	NO	YES	YES	YES	NO	NO	NO	
Tetraconazole	FU	*n.a.*	NO	NO	YES	YES	YES	NO	NO	NO	
Ziram	FU, RE	*n.a.*	NO	NO	NO	YES	YES	NO	YES (RE)	NO	
Sodium 5-nitroguaiacolate	PG	*n.a.*	*n.a.*	NO	NO	YES	YES	NO	YES	NO	
Sodium o-nitrophenolate	PG	*n.a.*	*n.a.*	NO	NO	YES	YES	NO	YES	NO	
Sodium p-nitrophenolate	PG	*n.a.*	*n.a.*	NO	NO	YES	YES	NO	YES	NO	
Benfluralin	HB	NO	NO	NO	NO	YES	YES	NO	NO	NO	
Flufenacet (formerly fluthiamide)	HB	NO	NO	NO	NO	YES	YES	NO	NO	NO	
Ioxynil	HB	NO	NO	NO	NO	YES	YES	NO	NO	NO	
Oxadiazon	HB	NO	NO	NO	NO	YES	YES	NO	NO	NO	
Profoxydim	HB	NO	NO	NO	NO	YES	YES	NO	NO	NO	
Prosulfocarb	HB	NO	NO	NO	NO	YES	YES	NO	NO	NO	
Terbuthylazine	HB	NO	NO	NO	NO	YES	YES	NO	NO	NO	
Tralkoxydim	HB	NO	NO	NO	NO	YES	YES	NO	NO	NO	
Beta-Cyfluthrin	IN	*n.a.*	NO	NO	NO	YES	YES	NO	NO	NO	
Cyfluthrin	IN, AC	*n.a.*	NO	NO	NO	YES	YES	NO	NO	NO	
Fenbuconazole	FU	*n.a.*	NO	NO	NO	YES	YES	NO	NO	NO	
Methomyl	IN	*n.a.*	NO	NO	NO	YES	YES	NO	NO	NO	
Diuron	HB	NO	NO	NO	NO	YES	NO	NO	NO	NO	
Molinate	HB	NO	NO	NO	NO	YES	NO	NO	NO	NO	
Oxadiargyl	HB	NO	NO	NO	NO	YES	NO	NO	NO	NO	
Carboxin	FU	*n.a.*	NO	NO	NO	YES	NO	NO	NO	NO	

Active Substance	Use Category	Different optional definitions of "low" as explained in the legend									
		<P1	<P2	<P5	<P10	<P20	<1SD	<2SD	<0.1 x median	<0.01 x median	≤0.001 mg/kg/d
Epoxiconazole	FU	*n.a.*	NO	NO	NO	YES	NO	NO	NO	NO	
Formetanate	IN, AC	*n.a.*	NO	NO	NO	YES	NO	NO	NO	NO	
Fuberidazole	FU	*n.a.*	NO	NO	NO	YES	NO	NO	NO	NO	
Pirimiphos-methyl	IN	*n.a.*	NO	NO	NO	YES	NO	NO	NO	NO	
Propineb	FU	*n.a.*	NO	NO	NO	YES	NO	NO	NO	NO	
Fenamiphos (aka phenamiphos)	NE	*n.a.*	*n.a.*	*n.a.*	*n.a.*	YES	NO	NO	NO	NO	YES*
Methiocarb (aka mercaptodimethur)	IN, MO, RE	*n.a.*	NO	NO	NO	NO	YES (RE)	NO	YES (RE)	NO	
Aluminium phosphide	IN, RO	*n.a.*	NO	NO	NO	NO	YES (RO)	NO	NO	NO	

Legend

- "Use category":
  Abbreviations for use categories are those used in the EU Pesticides Database.
- "<P1", "<P2", "<P5", "<P10", and "<P20":
  The ADI is defined to be "low", if the value is smaller than the 1%, 2%, 5%, 10%, or 20% percentile, respectively. Percentiles were calculated separately for every use category, including all active substances for which quantitative data were available in the relevant information sources.
- "<1SD" and "<2SD":
  The ADI is defined to be "low", if the value is smaller than the arithmetic mean of the log-transformed data minus 1 or 2 times the standard deviation (SD). Means and SDs were calculated separately for every use category, including all active substances for which quantitative data were available in the relevant information sources.
- "<0.1 x median" and "<0.01 x median":
  The ADI is defined to be "low", if the value is smaller than $1/10^{th}$ and $1/100^{th}$ of the median value, respectively. Medians were calculated separately for every use category, including all active substances for which quantitative data were available in the relevant information sources.
- "≤0.001 mg/kg/d":
  Across all use categories, the ADI is uniformly defined to be "low", if the value is smaller than or equal to 0.001 mg/kg/d.
- "YES" and "NO"
  indicate whether a substance fulfills or does not fulfill the respective definition of a "low ADI". If different use categories apply to one and the same substance, and if the CFS assessment gives inconsistent results for these different use categories, the use category or categories that drive the identification as a CFS are indicated in brackets after the "YES".
- "*n.a.*" = not applicable:
  1%, 2%, 5%, 10%, or 20% percentiles were calculated only if the data sets comprise a minimum of 100, 50, 20, 10, and 5 active substances, respectively. Otherwise, the application of this decision criterion was considered to be not meaningful, as explained in the main part of the report.
- "YES*":
  The substance is used as a nematicide (NE), exclusively or in addition to other uses (as indicated in the column "Use category"). NE is a small group (n = 8) with typically relatively low ADI values (median = 0.001 mg/kg/d). In this case, the uniform application of an absolute threshold value of "≤0.001 mg/kg/d" would identify 50% of all substances in this group as a CFS (57% of those for which quantitative data are available), thereby apparently conflicting with the legal requirement for an ADI that is "*significantly lower than those of the majority (…) within groups of substances/use categories*".

Table A 2 - Identification of CFS by low ARfD values

Active Substance	Use Category	Different optional definitions of "low" as explained in the legend									
		<P1	<P2	<P5	<P10	<P20	<1SD	<2SD	<0.1 x median	<0.01 x median	≤0.005 mg/kg/d
Dimoxystrobin	FU	*n.a.*	YES	YES	YES	YES	YES	YES	YES	NO	YES
Flurtamone	HB	*n.a.*	YES	YES	YES	YES	YES	YES	YES	NO	YES
Oxamyl	IN, NE	*n.a.*	*n.a.*	YES (IN)	YES (IN)	YES	YES	YES (IN)	YES (IN)	NO	YES*
Fluometuron	HB	*n.a.*	NO	YES	YES	YES	YES	NO	YES	NO	
Terbuthylazine	HB	*n.a.*	NO	YES	YES	YES	YES	NO	YES	NO	
Methomyl	IN	*n.a.*	*n.a.*	YES	YES	YES	YES	NO	YES	NO	YES
Bitertanol	FU	*n.a.*	NO	NO	YES	YES	YES	NO	NO	NO	
Diuron	HB	*n.a.*	NO	NO	YES	YES	YES	NO	NO	NO	
Metconazole	FU, PG	*n.a.*	NO	NO	YES	YES	YES	NO	NO	NO	
Prothioconazole	FU	*n.a.*	NO	NO	YES	YES	YES	NO	NO	NO	
Tralkoxydim	HB	*n.a.*	NO	NO	YES	YES	YES	NO	NO	NO	
Triazoxide	FU	*n.a.*	NO	NO	YES	YES	YES	NO	NO	NO	
Abamectin (aka avermectin)	AC, IN	*n.a.*	*n.a.*	NO	YES	YES	YES	NO	NO	NO	YES
Formetanate	IN, AC	*n.a.*	*n.a.*	NO	YES	YES	YES	NO	NO	NO	YES
Tefluthrin	IN	*n.a.*	*n.a.*	NO	YES	YES	YES	NO	NO	NO	YES
Pyraclostrobin	FU, PG	*n.a.*	NO	NO	YES (PG)	YES (PG)	NO	NO	NO	NO	
Methiocarb (aka mercaptodimethur)	IN, MO, RE	*n.a.*	*n.a.*	NO	NO	YES (RE)	YES (RE)	NO	NO	NO	
Dimethoate	IN, AC	*n.a.*	*n.a.*	NO	NO	YES (IN)	YES (AC)	NO	NO	NO	
Carbendazim	FU	*n.a.*	NO	NO	NO	YES	YES	NO	NO	NO	
Cyproconazole	FU	*n.a.*	NO	NO	NO	YES	YES	NO	NO	NO	
Epoxiconazole	FU	*n.a.*	NO	NO	NO	YES	YES	NO	NO	NO	
Fenpropidin	FU	*n.a.*	NO	NO	NO	YES	YES	NO	NO	NO	
Fluazifop-P	HB	*n.a.*	NO	NO	NO	YES	YES	NO	NO	NO	
Flufenacet (formerly fluthiamide)	HB	*n.a.*	NO	NO	NO	YES	YES	NO	NO	NO	
Fluquinconazole	FU	*n.a.*	NO	NO	NO	YES	YES	NO	NO	NO	
Glufosinate	HB	*n.a.*	NO	NO	NO	YES	YES	NO	NO	NO	
Mesotrione	HB	*n.a.*	NO	NO	NO	YES	YES	NO	NO	NO	
Metribuzin	HB	*n.a.*	NO	NO	NO	YES	YES	NO	NO	NO	
Prochloraz	FU	*n.a.*	NO	NO	NO	YES	YES	NO	NO	NO	
Fipronil	IN	*n.a.*	*n.a.*	NO	NO	YES	YES	NO	NO	NO	
lambda-Cyhalothrin	IN	*n.a.*	*n.a.*	NO	NO	YES	YES	NO	NO	NO	
Ethoprophos	NE, IN	*n.a.*	*n.a.*	NO	NO	YES (IN)	NO	NO	NO	NO	
Deltamethrin	IN	*n.a.*	*n.a.*	NO	NO	YES	NO	NO	NO	NO	
Aluminium phosphide	IN, RO	*n.a.*	*n.a.*	NO	NO	NO	YES (RO)	NO	NO	NO	
Acrinathrin	AC	*n.a.*	*n.a.*	*n.a.*	NO	NO	YES	NO	NO	NO	
Fenamiphos (aka phenamiphos)	NE	*n.a.*	*n.a.*	*n.a.*	NO	NO	NO	NO	NO	NO	YES*
Fosthiazate	NE	*n.a.*	*n.a.*	*n.a.*	NO	NO	NO	NO	NO	NO	YES*

Legend

- "Use category":
  Abbreviations for use categories are those used in the EU Pesticides Database.
- "<P1", "<P2", "<P5", "<P10", and "<P20":
  The ARfD is defined to be "low", if the value is smaller than the 1%, 2%, 5%, 10%, or 20%

percentile, respectively. Percentiles were calculated separately for every use category, including all active substances for which quantitative data were available in the relevant information sources.

- "<1SD" and "<2SD":
  The ARfD is defined to be "low", if the value is smaller than the arithmetic mean of the log-transformed data minus 1 or 2 times the standard deviation (SD). Means and SDs were calculated separately for every use category, including all active substances for which quantitative data were available in the relevant information sources.
- "<0.1 x median" and "<0.01 x median":
  The ARfD is defined to be "low", if the value is smaller than 1/10th and 1/100th of the median value, respectively. Medians were calculated separately for every use category, including all active substances for which quantitative data were available in the relevant information sources.
- "≤0.005 mg/kg/d":
  Across all use categories, the ARfD is uniformly defined to be "low", if the value is smaller than or equal to 0.005 mg/kg/d.
- "YES" and "NO"
  indicate whether a substance fulfills or does not fulfill the respective definition of a "low ARfD". If different use categories apply to one and the same substance, and if the CFS assessment gives inconsistent results for these different use categories, the use category or categories that drive the identification as a CFS are indicated in brackets after the "YES".
- "*n.a".* = not applicable:
  1%, 2%, 5%, 10%, or 20% percentiles were calculated only if the data sets comprise a minimum of 100, 50, 20, 10, and 5 active substances, respectively. Otherwise, the application of this decision criterion was considered to be not meaningful, as explained in the main part of the report.
- "YES*":
  The substance is used as a nematicide (NE), exclusively or in addition to other uses (as indicated in the column "Use category"). NE is a small group (n = 8) with typically relatively low ARfD values (median = 0.0075 mg/kg/d). In this case, the uniform application of an absolute threshold value of "≤0.005 mg/kg/d" would identify 38% of all substances in this group as a CFS (50% of those for which quantitative data are available), thereby apparently conflicting with the legal requirement for an ARfD that is "*significantly lower than those of the majority (…) within groups of substances/use categories*".

Table A 3 - Identification of CFS by low AOEL values

Active Substance	Use Category	Different optional definitions of "low" as explained in the legend									
		<P1	<P2	<P5	<P10	<P20	<1SD	<2SD	<0.1 x median	<0.01 x median	≤0.001 mg/kg/d
Sulcotrione	HB	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES
Ethoprophos	NE, IN	*n.a.*	NO	YES (IN)	YES (IN)	YES (IN)	YES (IN)	YES (IN)	YES (IN)	NO	YES*
Diquat (dibromide)	HB, DE	NO	NO	YES (HB)	YES (HB)	YES (HB)	YES (HB)	YES (HB)	YES (HB)	NO	YES***
Metam (incl. -potassium and -sodium)	FU, IN, HB, NE	NO	NO	YES (FU, HB, IN)	YES (FU, HB, IN)	YES (FU, HB, IN)	YES (FU, HB, IN)	YES (FU, HB, IN)	YES (FU, HB, IN)	NO	YES*
Dimethoate	IN, AC	*n.a.*	NO	YES	YES	YES	YES	YES (IN)	YES (IN)	NO	YES
Amitrole (aminotriazole)	HB	NO	NO	YES	YES	YES	YES	YES	YES	NO	YES
Fluquinconazole	FU	*n.a.*	NO	YES	YES	YES	YES	YES	YES	NO	YES
Triazoxide	FU	*n.a.*	NO	YES	YES	YES	YES	YES	YES	NO	YES
Diclofop	HB	NO	NO	YES	YES	YES	YES	NO	YES	NO	
Glufosinate	HB	NO	NO	YES	YES	YES	YES	NO	YES	NO	
Fluazinam	FU	*n.a.*	NO	YES	YES	YES	YES	NO	YES	NO	
Propineb	FU	*n.a.*	NO	YES	YES	YES	YES	NO	YES	NO	
Benfluralin	HB	NO	NO	NO	YES	YES	YES	NO	YES	NO	
Haloxyfop-P (Haloxyfop-R)	HB	NO	NO	NO	YES	YES	YES	NO	YES	NO	
Terbuthylazine	HB	NO	NO	NO	YES	YES	YES	NO	YES	NO	
Tralkoxydim	HB	NO	NO	NO	YES	YES	YES	NO	YES	NO	
Famoxadone	FU	*n.a.*	NO	NO	YES	YES	YES	NO	YES	NO	
Tefluthrin	IN	*n.a.*	NO	NO	YES	YES	YES	NO	YES	NO	
Sodium 5-nitroguaiacolate	PG	*n.a.*	*n.a.*	NO	YES	YES	YES	NO	YES	NO	
Sodium o-nitrophenolate	PG	*n.a.*	*n.a.*	NO	YES	YES	YES	NO	YES	NO	
Sodium p-nitrophenolate	PG	*n.a.*	*n.a.*	NO	YES	YES	YES	NO	YES	NO	
Abamectin (aka avermectin)	AC, IN	*n.a.*	NO	NO	YES (AC)	YES	YES	NO	NO	NO	
Oxadiargyl	HB	NO	NO	NO	YES	YES	YES	NO	NO	NO	
Epoxiconazole	FU	*n.a.*	NO	NO	YES	YES	YES	NO	NO	NO	
Fenpropimorph	FU	*n.a.*	NO	NO	YES	YES	YES	NO	NO	NO	
Flusilazole	FU	*n.a.*	NO	NO	YES	YES	YES	NO	NO	NO	
Fuberidazole	FU	*n.a.*	NO	NO	YES	YES	YES	NO	NO	NO	
Bromadiolone	RO	*n.a.*	*n.a.*	*n.a.*	*n.a.*	YES	YES	NO	YES	YES	YES**
Difenacoum	RO	*n.a.*	*n.a.*	*n.a.*	*n.a.*	YES	YES	NO	YES	YES	YES**
Metconazole	FU, PG	*n.a.*	NO	NO	NO	YES	YES (PG)	NO	NO	NO	
Pyraclostrobin	FU, PG	*n.a.*	NO	NO	NO	YES	YES (PG)	NO	NO	NO	
Formetanate	IN, AC	*n.a.*	NO	NO	NO	YES	YES (IN)	NO	NO	NO	
Bromoxynil	HB	NO	NO	NO	NO	YES	YES	NO	NO	NO	
Diuron	HB	NO	NO	NO	NO	YES	YES	NO	NO	NO	
Fluometuron	HB	NO	NO	NO	NO	YES	YES	NO	NO	NO	
Ioxynil	HB	NO	NO	NO	NO	YES	YES	NO	NO	NO	
Linuron	HB	NO	NO	NO	NO	YES	YES	NO	NO	NO	
Molinate	HB	NO	NO	NO	NO	YES	YES	NO	NO	NO	
Prosulfocarb	HB	NO	NO	NO	NO	YES	YES	NO	NO	NO	
Quizalofop-P	HB	NO	NO	NO	NO	YES	YES	NO	NO	NO	
Chlorothalonil	FU	*n.a.*	NO	NO	NO	YES	YES	NO	NO	NO	
Fipronil	IN	*n.a.*	NO	NO	NO	YES	YES	NO	NO	NO	
Indoxacarb	IN	*n.a.*	NO	NO	NO	YES	YES	NO	NO	NO	
lambda-Cyhalothrin	IN	*n.a.*	NO	NO	NO	YES	YES	NO	NO	NO	
Methomyl	IN	*n.a.*	NO	NO	NO	YES	YES	NO	NO	NO	
Pyridaben	AC, IN	*n.a.*	NO	NO	NO	YES (IN)	NO	NO	NO	NO	
Dazomet	NE, FU, HB, ST	NO	NO	NO	NO	YES (FU)	NO	NO	NO	NO	

Active Substance	Use Category	Different optional definitions of "low" as explained in the legend									
		<P1	<P2	<P5	<P10	<P20	<1SD	<2SD	<0.1 x median	<0.01 x median	≤0.001 mg/kg/d
Ziram	FU, RE	*n.a.*	NO	NO	NO	YES (FU)	NO	NO	NO	NO	
Fenoxaprop-P	HB	NO	NO	NO	NO	YES	NO	NO	NO	NO	
Oxasulfuron	HB	NO	NO	NO	NO	YES	NO	NO	NO	NO	
Oxyfluorfen	HB	NO	NO	NO	NO	YES	NO	NO	NO	NO	
Bitertanol	FU	*n.a.*	NO	NO	NO	YES	NO	NO	NO	NO	
Cymoxanil	FU	*n.a.*	NO	NO	NO	YES	NO	NO	NO	NO	
Diflubenzuron	IN	*n.a.*	NO	NO	NO	YES	NO	NO	NO	NO	
Dithianon	FU	*n.a.*	NO	NO	NO	YES	NO	NO	NO	NO	
Iprovalicarb	FU	*n.a.*	NO	NO	NO	YES	NO	NO	NO	NO	
Bifenazate	AC	*n.a.*	*n.a.*	NO	NO	YES	NO	NO	NO	NO	
Aluminium ammonium sulphate	RE	*n.a.*	*n.a.*	*n.a.*	*n.a.*	YES	NO	NO	NO	NO	
Fenamiphos (aka phenamiphos)	NE	*n.a.*	*n.a.*	*n.a.*	*n.a.*	YES	NO	NO	NO	NO	YES*
Warfarin (aka coumaphene)	RO	*n.a.*	*n.a.*	*n.a.*	*n.a.*	NO	NO	NO	YES	NO	YES**

Legend

- "Use category":
  Abbreviations for use categories are those used in the EU Pesticides Database.
- "<P1", "<P2", "<P5", "<P10", and "<P20":
  The AOEL is defined to be "low", if the value is smaller than the 1%, 2%, 5%, 10%, or 20% percentile, respectively. Percentiles were calculated separately for every use category, including all active substances for which quantitative data were available in the relevant information sources.
- "<1SD" and "<2SD":
  The AOEL is defined to be "low", if the value is smaller than the arithmetic mean of the log-transformed data minus 1 or 2 times the standard deviation (SD). Means and SDs were calculated separately for every use category, including all active substances for which quantitative data were available in the relevant information sources.
- "<0.1 x median" and "<0.01 x median":
  The AOEL is defined to be "low", if the value is smaller than $1/10^{th}$ and $1/100^{th}$ of the median value, respectively. Medians were calculated separately for every use category, including all active substances for which quantitative data were available in the relevant information sources.
- "≤0.001 mg/kg/d":
  Across all use categories, the AOEL is uniformly defined to be "low", if the value is smaller than or equal to 0.001 mg/kg/d.
- "YES" and "NO"
  indicate whether a substance fulfills or does not fulfill the respective definition of a "low AOEL". If different use categories apply to one and the same substance, and if the CFS assessment gives inconsistent results for these different use categories, the use category or categories that drive the identification as a CFS are indicated in brackets after the "YES".
- "*n.a.*" = not applicable:
  1%, 2%, 5%, 10%, or 20% percentiles were calculated only if the data sets comprise a minimum of 100, 50, 20, 10, and 5 active substances, respectively. Otherwise, the application of this decision criterion was considered to be not meaningful, as explained in the main part of the report.
- "YES*":
  The substance is used as a nematicide (NE), exclusively or in addition to other uses (as indicated in

the column "Use category"). NE is a small group (n = 8) with typically relatively low AOEL values (median = 0.005 mg/kg/d). In this case, the uniform application of an absolute threshold value of "≤0.001 mg/kg/d" would identify 38% of all substances in this group as a CFS (43% of those for which quantitative data are available), thereby apparently conflicting with the legal requirement for an AOEL that is "*significantly lower than those of the majority (…) within groups of substances/use categories*".

- "YES**":
  The substance is exclusively used as a rodenticide (RE), a small group (n = 8) with typically relatively low AOEL values (median = 0.0019 mg/kg/d). In this case, the uniform application of an absolute threshold value of "≤0.001 mg/kg/d" would identify 38% of all substances in this group as a CFS (43% of those for which quantitative data are available), thereby apparently conflicting with the legal requirement for an AOEL that is "*significantly lower than those of the majority (…) within groups of substances/use categories*".
- "YES***":
  in addition to the use as a herbicide (HB), the substance is used as a desiccant (DE), and it is the only substance that is approved for that purpose. As a consequence, the uniform application of an absolute threshold value of "≤0.001 mg/kg/d" across all use groups would identify 100% of the substances in the DE group as a CFS, thereby apparently conflicting with the legal requirement for an AOEL that is "*significantly lower than those of the majority (…) within groups of substances/use categories*", unless DE and HB would be clustered in a single group.

Table A 4 - List of active substances that fulfil the persistence criterion as their half-life in marine water is higher than 60 days

No data available

Table A 5 - List of active substances that fulfil the persistence criterion as their half-life in fresh and estuarine water is higher than 40 days

Substance	CAS number
Amitrole (aminotriazole)	61-82-5
Bentazone	25057-89-0
Bispyribac	125401-75-4
Bromadiolone	28772-56-7
Chloridazon (aka pyrazone)	1698-60-8
Chlorotoluron (unstated stereochemistry)	15545-48-9
Clodinafop	114420-56-3
Clomazone	81777-89-1
Clopyralid	1702-17-6
Clothianidin	210880-92-5
Cyproconazole	94361-06-5
Dicamba	1918-00-9
Epoxiconazole	135319-73-2 (formerly 106325-08-0)
Ethofumesate	26225-79-6
Fipronil	120068-37-3
Fluazifop-P	83066-88-0 (Fluazifop-P)
Flufenacet (formerly fluthiamide)	142459-58-3
Fluometuron	2164-17-2
Fluoxastrobin	361377-29-9
Flutolanil	66332-96-5
Fosthiazate	98886-44-3
Gibberellic acid	77-06-5
Haloxyfop-P (Haloxyfop-R)	Acid: 95977-29-0 Ester: 72619-32-0
Imazamox	114311-32-9
Imazaquin	81335-37-7
Imazosulfuron	122548-33-8
Iprovalicarb	140923-17-7
Isoproturon	34123-59-6
Mecoprop	7085-19-0
Mecoprop-P	16484-77-8
Mesosulfuron	400852-66-6
Metaldehyde	108-62-3 (tetramer) 9002-91-9 (homopolymer)
Metazachlor	67129-08-2
Methyl nonyl ketone	112-12-9
Metribuzin	21087-64-9

Substance	CAS number
Metsulfuron-methyl	74223-64-6
Nicosulfuron	111991-09-4
Oxyfluorfen	42874-03-3
Paclobutrazol	76738-62-0
Pirimicarb	23103-98-2
Propoxycarbazone	145026-81-9
Prosulfuron	94125-34-5
Tebufenpyrad	119168-77-3
Tepraloxydim	149979-41-9
Thifensulfuron-methyl	79277-27-3
Tralkoxydim	87820-88-0
Triadimenol	55219-65-3
Triasulfuron	126535-15-7 Reg. indicates: 82097-50-5
Triticonazole	131983-72-7
Tritosulfuron	142469-14-5

Table A 6 - List of active substances that fulfil the persistence criterion as their half-life in marine sediments is higher than 180 days

No data available

Table A 7 - List of active substances that fulfil the persistence criterion as their half-life in marine fresh and estuarine water sediments is higher than 120 days

Substance	CAS number
8-Hydroxyquinoline incl. oxyquinoleine	148-24-3 (8-hydroxyquinoline)
Azimsulfuron	120162-55-2
Azoxystrobin	131860-33-8
Benalaxyl	71626-11-4
Bentazone	25057-89-0
Bifenthrin	82657-04-3
Bordeaux mixture (copper compounds)	8011-63-0
Boscalid (formerly nicobifen)	188425-85-6
Bromadiolone	28772-56-7
Bromuconazole	116255-48-2
Chloridazon (aka pyrazone)	1698-60-8
Chlorotoluron (unstated stereochemistry)	15545-48-9
Copper compounds	Copper hydroxide CAS No 20427-59-2 Copper oxychloride CAS No 1332-65-6 or 1332-40-7 Copper oxide CAS No 1317-39-1 Bordeaux mixture 8011-63-0 Tribasic copper sulphate CAS No 12527-76-3
Copper hydroxide	20427-59-2
Copper oxide	1317-39-1
Copper oxychloride	1332-65-6 or 1332-40-7
Cyproconazole	94361-06-5
Cyprodinil	121522-61-2
Cyromazine	66215-27-8
Difenoconazole	119446-68-3
Diflufenican	83164-33-4
Dimoxystrobin	149961-52-4
Epoxiconazole	135319-73-2 (formerly 106325-08-0)
Ethofumesate	26225-79-6
Fenamidone	161326-34-7
Fenbuconazole	114369-43-6
Fenbutatin oxide	13356-08-6
Fludioxonil	131341-86-1
Flumioxazine	103361-09-7
Fluometuron	2164-17-2
Fluopicolide	239110-15-7
Fluoxastrobin	361377-29-9

Substance	CAS number
Flutolanil	66332-96-5
Fluxapyroxad	907204-31-3
Forchlorfenuron	68157-60-8
Glyphosate (incl trimesium aka sulfosate)	1071-83-6
Imazalil (aka enilconazole)	35554-44-0 73790-28-0 (replaced)
Imazamox	114311-32-9
Imazaquin	81335-37-7
Imazosulfuron	122548-33-8
Imidacloprid	138261-41-3
Isoproturon	34123-59-6
Isopyrazam	881685-58-1
Metconazole	125116-23-6 (unstated stereo-chemistry)
Methoxyfenozide	161050-58-4
Methyl nonyl ketone	112-12-9
Metsulfuron-methyl	74223-64-6
Myclobutanil	88671-89-0
Napropamide	15299-99-7
Oxadiazon	19666-30-9
Paclobutrazol	76738-62-0
Penconazole	66246-88-6
Pencycuron	66063-05-6
Picloram	1918-02-1
Pirimicarb	23103-98-2
Prochloraz	67747-09-5
Propiconazole	60207-90-1
Propoxycarbazone	145026-81-9
Prosulfocarb	52888-80-9
Prosulfuron	94125-34-5
Pyrimethanil	53112-28-0
Quinmerac	90717-03-6
Quinoxyfen	124495-18-7
Sintofen (aka Cintofen)	130561-48-7
S-metolachlor	87392-12-9
Spinosad	131929-60-7 (Spinosyn A) 131929-63-0 (Spinosyn D)
Tebuconazole	107534-96-3

Table A 8 - List of active substances that fulfil the persistence criterion as their half-life in marine fresh and estuarine water sediments is higher than 120 days

Substance	CAS number
8-Hydroxyquinoline incl. oxyquinoleine	148-24-3 (8-hydroxyquinoline)
Azimsulfuron	120162-55-2
Azoxystrobin	131860-33-8
Benalaxyl	71626-11-4
Bentazone	25057-89-0
Bifenthrin	82657-04-3
Bordeaux mixture (copper compounds)	8011-63-0
Boscalid (formerly nicobifen)	188425-85-6
Bromadiolone	28772-56-7
Bromuconazole	116255-48-2
Chloridazon (aka pyrazone)	1698-60-8
Chlorotoluron (unstated stereochemistry)	15545-48-9
Copper compounds	Copper hydroxide CAS No 20427-59-2 Copper oxychloride CAS No 1332-65-6 or 1332-40-7 Copper oxide CAS No 1317-39-1 Bordeaux mixture 8011-63-0 Tribasic copper sulphate CAS No 12527-76-3
Copper hydroxide	20427-59-2
Copper oxide	1317-39-1
Copper oxychloride	1332-65-6 or 1332-40-7
Cyproconazole	94361-06-5
Cyprodinil	121522-61-2
Cyromazine	66215-27-8
Difenoconazole	119446-68-3
Diflufenican	83164-33-4
Dimoxystrobin	149961-52-4
Epoxiconazole	135319-73-2 (formerly 106325-08-0)
Ethofumesate	26225-79-6
Fenamidone	161326-34-7
Fenbuconazole	114369-43-6
Fenbutatin oxide	13356-08-6
Fludioxonil	131341-86-1
Flumioxazine	103361-09-7
Fluometuron	2164-17-2
Fluopicolide	239110-15-7
Fluoxastrobin	361377-29-9

Substance	CAS number
Flutolanil	66332-96-5
Fluxapyroxad	907204-31-3
Forchlorfenuron	68157-60-8
Glyphosate (incl trimesium aka sulfosate)	1071-83-6
Imazalil (aka enilconazole)	35554-44-0 73790-28-0 (replaced)
Imazamox	114311-32-9
Imazaquin	81335-37-7
Imazosulfuron	122548-33-8
Imidacloprid	138261-41-3
Isoproturon	34123-59-6
Isopyrazam	881685-58-1
Metconazole	125116-23-6 (unstated stereo-chemistry)
Methoxyfenozide	161050-58-4
Methyl nonyl ketone	112-12-9
Metsulfuron-methyl	74223-64-6
Myclobutanil	88671-89-0
Napropamide	15299-99-7
Oxadiazon	19666-30-9
Paclobutrazol	76738-62-0
Penconazole	66246-88-6
Pencycuron	66063-05-6
Picloram	1918-02-1
Pirimicarb	23103-98-2
Prochloraz	67747-09-5
Propiconazole	60207-90-1
Propoxycarbazone	145026-81-9
Prosulfocarb	52888-80-9
Prosulfuron	94125-34-5
Pyrimethanil	53112-28-0
Quinmerac	90717-03-6
Quinoxyfen	124495-18-7
Sintofen (aka Cintofen)	130561-48-7
S-metolachlor	87392-12-9
Spinosad	131929-60-7 (Spinosyn A) 131929-63-0 (Spinosyn D)
Tebuconazole	107534-96-3

Table A 9 - List of active substances that fulfil the persistence criterion as their biodegradation (aerobic) half-life in soil is higher than 120 days

Substance	CAS number
Boscalid (formerly nicobifen)	188425-85-6
Bromuconazole	116255-48-2
Cyproconazole	94361-06-5
Cyprodinil	121522-61-2
Diflufenican	83164-33-4
Diquat (dibromide)	2764-72-9 (ion), 85-00-7 (dibromide)
Epoxiconazole	135319-73-2 (formerly 106325-08-0)
Esfenvalerate	66230-04-4
Fluometuron	2164-17-2
Fluopicolide	239110-15-7
Fluquinconazole	136426-54-5
Flutriafol	76674-21-0
Fluxapyroxad	907204-31-3
Imidacloprid	138261-41-3
Iprodione	36734-19-7
Lufenuron	103055-07-8
Metconazole	125116-23-6 (unstated stereo-chemistry)
Methoxyfenozide	161050-58-4
Metrafenone	220899-03-6
Myclobutanil	88671-89-0
Napropamide	15299-99-7
Oxadiazon	19666-30-9
Pendimethalin	40487-42-1
Propiconazole	60207-90-1
Quinoxyfen	124495-18-7
S-metolachlor	87392-12-9
Tetraconazole	112281-77-3
Thiabendazole	148-79-8
Triticonazole	131983-72-7
Ziram	137-30-4

Table A 10 - List of active substances that fulfil the bioaccumulation criterion as their bioaccumulation factor (BCF) in aquatic species is higher than 2,000

Substance	CAS number
Aclonifen	74070-46-5
Benfluralin	1861-40-1
Bifenthrin	82657-04-3
Chlorothalonil	1897-45-6
Diclofop	CAS No 40843-25-2 (parent) CAS No 257-141-8 (diclofop-methyl)
Difenacoum	56073-07-5
Esfenvalerate	66230-04-4
Etofenprox	80844-07-1
Etoxazole	153233-91-1
Famoxadone	131807-57-3
Fenpyroximate	134098-61-6
lambda-cyhalothrin	91465-08-6
Lufenuron	103055-07-8
Oxyfluorfen	42874-03-3
Pendimethalin	40487-42-1
Quinoxyfen	124495-18-7
Triflusulfuron	126535-15-7

Table A 11 - List of active substances that fulfil the toxicity criterion as their long term no-observed effect (NOEC) for marine and freshwater organism (fish) is less than 0.01 mg/L

Substance	CAS number
1-Decanol	112-30-1
Abamectin (aka avermectin)	71751-41-2
Aclonifen	74070-46-5
Acrinathrin	101007-06-1
Alpha-Cypermethrin (aka alphamethrin)	67375-30-8
Azadirachtin	11141-17-6 (azadirachtin A)
Benfluralin	1861-40-1
Beta-cyfluthrin	68359-37-5 (unstated stereochemistry)
Bifenox	42576-02-3
Bifenthrin	82657-04-3
Bitertanol	55179-31-2
Bordeaux mixture (copper compounds)	8011-63-0
Chlorpyrifos	2921-88-2
Chlorpyrifos-methyl	5598-13-0
Clofentezine	74115-24-5
Copper compounds	Copper hydroxide CAS No 20427-59-2 Copper oxychloride CAS No 1332-65-6 or 1332-40-7 Copper oxide CAS No 1317-39-1 Bordeaux mixture 8011-63-0 Tribasic copper sulphate CAS No 12527-76-3
Copper hydroxide	20427-59-2
Copper oxide	1317-39-1
Copper oxychloride	1332-65-6 or 1332-40-7
Cyfluthrin	68359-37-5 (unstated stereochemistry)
Cypermethrin	52315-07-8
Deltamethrin	52918-63-5
Difenacoum	56073-07-5
Etofenprox	80844-07-1
Famoxadone	131807-57-3
Fenamiphos (aka phenamiphos)	22224-92-6
Fenazaquin	120928-09-8
Fenbuconazole	114369-43-6
Fenbutatin oxide	13356-08-6
Fenpropimorph	67564-91-4
Fenpyroximate	134098-61-6
Fipronil	120068-37-3

Substance	CAS number
Fluazinam	79622-59-6
Haloxyfop-P (Haloxyfop-R)	Acid: 95977-29-0 Ester: 72619-32-0
Isopyrazam	881685-58-1
Kresoxim-methyl	143 390-89-0
lambda-cyhalothrin	91465-08-6
Malathion	121-75-5
Maneb	12427-38-2
Metam (incl. -potassium and -sodium)	144-54-7
Metconazole	125116-23-6 (unstated stereo-chemistry)
Milbemectin	Milbemectin is a mixture of M.A3 and M.A4 M.A3: 51596-10-2 M.A4: 51596-11-3
Oxadiazon	19666-30-9
Pendimethalin	40487-42-1
Phosmet	732-11-6
Picolinafen	137641-05-5
Proquinazid	189278-12-4
Pyraclostrobin	175013-18-0
Pyrethrins	8003-34-7
Pyriproxyfen	95737-68-1
Spirodiclofen	148477-71-8
Tau-fluvalinate	102851-06-9
Tebufenpyrad	119168-77-3
Tefluthrin	79538-32-2
Thiabendazole	148-79-8
Triazoxide	72459-58-6
Trifloxystrobin	141517-21-7
zeta-Cypermethrin	52315-07-8
Zoxamide	156052-68-5

Table A 12 - List of active substances that fulfil the toxicity criterion as their long term no-observed effect (NOEC) for marine and freshwater organism (algae) is less than 0.01 mg/L

Substance	CAS number
Aclonifen	74070-46-5
Azimsulfuron	120162-55-2
Beflubutamid	113614-08-7
Bordeaux mixture (copper compounds)	8011-63-0
Bromuconazole	116255-48-2
Carfentrazone-ethyl	128639-02.1
Chlorotoluron (unstated stereochemistry)	15545-48-9
Chlorsulfuron	64902-72-3
Cinidon ethyl	142891-20-1
Copper compounds	Copper hydroxide CAS No 20427-59-2 Copper oxychloride CAS No 1332-65-6 or 1332-40-7 Copper oxide CAS No 1317-39-1 Bordeaux mixture 8011-63-0 Tribasic copper sulphate CAS No 12527-76-3
Copper hydroxide	20427-59-2
Copper oxide	1317-39-1
Copper oxychloride	1332-65-6 or 1332-40-7
Cyflufenamid	180409-60-3
Cyproconazole	94361-06-5
Desmedipham	13684-56-5
Didecyldimethylammonium chloride	not allocated
Diflufenican	83164-33-4
Dimethachlor	50563-36-5
Dimethenamid-P	163515-14-8
Dimoxystrobin	149961-52-4
Dodine	2439-10-3
Epoxiconazole	135319-73-2 (formerly 106325-08-0)
Famoxadone	131807-57-3
Fenbutatin oxide	13356-08-6
Fenpropidin	67306-00-7
Fenpropimorph	67564-91-4
Fenpyroximate	134098-61-6
Fipronil	120068-37-3
Flazasulfuron	104040-78-0
Florasulam	145701-23-1
Fludioxonil	131341-86-1
Flufenacet (formerly fluthiamide)	142459-58-3

Substance	CAS number
Flumioxazine	103361-09-7
Fluopicolide	239110-15-7
Flupyrsulfuron-methyl (DPX KE 459)	144740-54-5
Fluquinconazole	136426-54-5
Flurochloridone	61213-25-0
Flurtamone	96525-23-4
Imazamox	114311-32-9
Isoxaflutole	141112-29-0
Lenacil	2164-08-1
Linuron	330-55-2
Lufenuron	103055-07-8
Maneb	12427-38-2
Methomyl	16752-77-50
Metiram	9006-42-2
Metosulam	139528-85-1
Metribuzin	21087-64-9
Metsulfuron-methyl	74223-64-6
Oryzalin	19044-88-3
Oxadiargyl	39807-15-3
Oxadiazon	19666-30-9
Pencycuron	66063-05-6
Pendimethalin	40487-42-1
Penoxsulam	219714-96-2
Pethoxamid	106700-29-2
Phenmedipham	13684-63-4
Picolinafen	137641-05-5
Prochloraz	67747-09-5
Propiconazole	60207-90-1
Prosulfocarb	52888-80-9
Prosulfuron	94125-34-5
Quinmerac	90717-03-6
Quinoclamine	2797-51-5
Quinoxyfen	124495-18-7
S-metolachlor	87392-12-9
Spinosad	131929-60-7 (Spinosyn A) 131929-63-0 (Spinosyn D)
Spirodiclofen	148477-71-8
Spiroxamine	1181134-30-8
Teflubenzuron	83121-18-0
Terbuthylazine	5915-41-3
Thifensulfuron-methyl	79277-27-3
Thiram	137-26-8
Tri-allate	2303-17-5

Substance	CAS number
Triasulfuron	126535-15-7 Reg. indicates: 82097-50-5
Triazoxide	72459-58-6
Tribenuron (aka metometuron)	106040-48-6 (tribenuron)
Trifloxystrobin	141517-21-7
Triflumuron	64628-44-0
Triflusulfuron	126535-15-7
Zinc phosphide	1314-84-7
Ziram	137-30-4
Zoxamide	156052-68-5

Table A 13 - List of active substances that fulfil the toxicity criterion as their long term no-observed effect (NOEC) for marine and freshwater organism (*Daphnia*) is less than 0.01 mg/L

Substance	CAS number
Abamectin (aka avermectin)	71751-41-2
Acrinathrin	101007-06-1
Alpha-Cypermethrin (aka alphamethrin)	67375-30-8
Beta-cyfluthrin	68359-37-5 (unstated stereochemistry)
Bifenox	42576-02-3
Bifenthrin	82657-04-3
Bordeaux mixture (copper compounds)	8011-63-0
Bromuconazole	116255-48-2
Carbendazim	10605-21-7
Chlorpyrifos	2921-88-2
Chlorpyrifos-methyl	5598-13-0
Clethodim	99129-21-2
Copper compounds	Copper hydroxide CAS No 20427-59-2 Copper oxychloride CAS No 1332-65-6 or 1332-40-7 Copper oxide CAS No 1317-39-1 Bordeaux mixture 8011-63-0 Tribasic copper sulphate CAS No 12527-76-3
Copper hydroxide	20427-59-2
Copper oxide	1317-39-1
Copper oxychloride	1332-65-6 or 1332-40-7
Cyfluthrin	68359-37-5 (unstated stereochemistry)
Cypermethrin	52315-07-8
Cyprodinil	121522-61-2
Deltamethrin	52918-63-5
Desmedipham	13684-56-5
Didecyldimethylammonium chloride	not allocated
Dodine	2439-10-3
Ethoprophos	13194-48-4
Etofenprox	80844-07-1
Etoxazole	153233-91-1
Famoxadone	131807-57-3
Fenamiphos (aka phenamiphos)	22224-92-6
Fenazaquin	120928-09-8

Substance	CAS number
Fenbutatin oxide	13356-08-6
Fenoxycarb	79127-80-3
Fenpyroximate	134098-61-6
Fipronil	120068-37-3
Fludioxonil	131341-86-1
Formetanate	23422-53-9
Hexythiazox	78587-05-0
lambda-cyhalothrin	91465-08-6
Lufenuron	103055-07-8
Malathion	121-75-5
Mancozeb	8018-01-7 (formerly 8065-67-5)
Maneb	12427-38-2
Metam (incl. -potassium and -sodium)	144-54-7
Methiocarb (aka mercaptodimethur)	2032-65-7
Methomyl	16752-77-50
Metiram	9006-42-2
Milbemectin	Milbemectin is a mixture of M.A3 and M.A4 M.A3: 51596-10-2 M.A4: 51596-11-3
Oxyfluorfen	42874-03-3
Phosmet	732-11-6
Picolinafen	137641-05-5
Pirimicarb	23103-98-2
Pirimiphos-methyl	29232-93-7
Proquinazid	189278-12-4
Pyraclostrobin	175013-18-0
Pyrethrins	8003-34-7
Pyridate	55512-33.9
Pyriproxyfen	95737-68-1
Quinoclamine	2797-51-5
Spinosad	131929-60-7 (Spinosyn A) 131929-63-0 (Spinosyn D)
Tau-fluvalinate	102851-06-9
Tebufenpyrad	119168-77-3
Teflubenzuron	83121-18-0
Tefluthrin	79538-32-2
Thiram	137-26-8
Trifloxystrobin	141517-21-7

Substance	CAS number
Triflumuron	64628-44-0
zeta-Cypermethrin	52315-07-8
Ziram	137-30-4

Table A 14 - List of active substances that fulfil the toxicity criterion as their long term no-observed effect (NOEC) for marine and freshwater organism (Other than fish or algae or Daphnia) is less than 0.01 mg/L

Substance	CAS number
Aclonifen	74070-46-5
Amidosulfuron	120923-37-7
Azimsulfuron	120162-55-2
Beflubutamid	113614-08-7
Benfluralin	1861-40-1
Bifenox	42576-02-3
Bispyribac	125401-75-4
Carfentrazone-ethyl	128639-02.1
Chlorotoluron (unstated stereochemistry)	15545-48-9
Chlorsulfuron	64902-72-3
Cinidon ethyl	142891-20-1
Diflufenican	83164-33-4
Dimethachlor	50563-36-5
Dimethenamid-P	163515-14-8
Ethoxysulfuron	126801-58-9
Flazasulfuron	104040-78-0
Florasulam	145701-23-1
Flumioxazine	103361-09-7
Flupyrsulfuron-methyl (DPX KE 459)	144740-54-5
Flurochloridone	61213-25-0
Flurtamone	96525-23-4
Foramsulfuron	173159-57-4
Imazamox	114311-32-9
Imazaquin	81335-37-7
Imazosulfuron	122548-33-8
Ioxynil	13684-83-4
Isoxaben	82558-50-7
Isoxaflutole	141112-29-0
Lenacil	2164-08-1
Linuron	330-55-2
Mesotrione	104206-8
Metribuzin	21087-64-9
Metsulfuron-methyl	74223-64-6
Nicosulfuron	111991-09-4
Oryzalin	19044-88-3
Oxadiargyl	39807-15-3

Substance	CAS number
Oxadiazon	19666-30-9
Oxasulfuron	144651-06-9
Oxyfluorfen	42874-03-3
Paclobutrazol	76738-62-0
Pendimethalin	40487-42-1
Penoxsulam	219714-96-2
Pethoxamid	106700-29-2
Picolinafen	137641-05-5
Propoxycarbazone	145026-81-9
Prosulfuron	94125-34-5
Quinoclamine	2797-51-5
Rimsulfuron (aka renriduron)	122931-48-0 (rimsulfuron)
S-metolachlor	87392-12-9
Sulcotrione	99105-77-8
Sulfosulfuron	141776-32-1
Terbuthylazine	5915-41-3
Thifensulfuron-methyl	79277-27-3
Triasulfuron	126535-15-7 Reg. indicates: 82097-50-5
Tribenuron (aka metometuron)	106040-48-6 (tribenuron)
Triflusulfuron	126535-15-7

Table A 15 - List of active substances classified as CFS as they contain a significant proportion of inactive isomers (Condition 4)

Substance	CAS number
Mecoprop	7085-19-0
Metalaxyl	57837-19-1

Table A 16 - List of active substances classified as Carcinogenic (Category 1A or 1B)

No active substances

Table A 17 - List of active substances to be classified as Carcinogenic (Category 1A or 1B)

No active substances

Table A 18 - List of active substances classified as Carcinogenic (Category 2)

Substance	CAS number
Captan	133-06-02
Chlorothalonil	1897-45-6
Chlorotoluron (unstated stereochemistry)	15545-48-9
Chlorpropham	101-21-3
Cinidon ethyl	142891-20-1
Dimoxystrobin	149961-52-4
Diuron	330-54-1
Epoxiconazole	135319-73-2 (formerly 106325-08-0)
Etridiazole	2593-15-9
Flusilazole	85509-19-9
Folpet	133-07-3
Forchlorfenuron	68157-60-8
Iprodione	36734-19-7
Isoproturon	34123-59-6
Kresoxim-methyl	143 390-89-0
Linuron	330-55-2
Mepanipyrim	110235-47-7
Molinate	2212-67-1
Profoxydim	139001- 49-3
Propyzamide	23950-58-5
Pymetrozine	123312-89-0
Tepraloxydim	149979-41-9

Table A 19 - List of active substances to be classified as Carcinogenic (Category 2)

Substance	CAS number
Aclonifen	74070-46-5
Bifenthrin	82657-04-3
Carboxin	5234-68-4
Fenoxycarb	79127-80-3
Fuberidazole	3878-19-1
Imazalil (aka enilconazole)	35554-44-0 73790-28-0 (replaced)
Metazachlor	67129-08-2
Metosulam	139528-85-1
Proquinazid	189278-12-4
Quizalofop-P-tefuryl	119738-06-6
Terbuthylazine	5915-41-3
Thiacloprid	111988-49-9
Tralkoxydim	87820-88-0

Table A 20 - List of active substances classified as Mutagenic (Category 1A or 1B)

Substance	CAS number
Carbendazim	10605-21-7

Table A 21 - List of active substances classified as Mutagenic (Category 2)

Substance	CAS number
Quizalofop-P	100646-51-3
Thiophanate-methyl (unstated stereochemistry)	23564-05-8

Table A 22 - List of active substances classified as Toxic for reproduction (Category 1A or 1B)

1A	Substance	CAS number
1	Oxadiargyl	39807-15-3
2	Warfarin (aka coumaphene)	81-81-2

1B	Substance	CAS number
1	Carbendazim	10605-21-7
2	Flumioxazine	103361-09-7
3	Flusilazole	85509-19-9
4	Glufosinate	77182-82-2
5	Linuron	330-55-2
6	Quizalofop-P-tefuryl	119738-06-6

Table A 23 - List of active substances to be classified as Toxic for reproduction (Category 1A or 1B)

Substance	CAS number
Epoxiconazole	135319-73-2 (formerly 106325-08-0)

Table A 24 - List of active substances classified as Toxic for reproduction (Category 2)

Substance	CAS number
Amitrole (aminotriazole)	61-82-5
Bromoxynil	1689-84-5
Chlorotoluron (unstated stereochemistry)	15545-48-9
Cyproconazole	94361-06-5
Dimoxystrobin	149961-52-4
Epoxiconazole	135319-73-2 (formerly 106325-08-0)
Fenpropimorph	67564-91-4
Ioxynil	13684-83-4
Isoxaflutole	141112-29-0
Mancozeb	8018-01-7 (formerly 8065-67-5)
Maneb	12427-38-2
Metconazole	125116-23-6 (unstated stereo-chemistry)
Molinate	2212-67-1
Myclobutanil	88671-89-0
Profoxydim	139001- 49-3
Tebuconazole	107534-96-3
Tepraloxydim	149979-41-9

Table A 25 - List of active substances to be classified as Toxic for reproduction (Category 2)

Substance	CAS number
8-Hydroxyquinoline incl. oxyquinoleine	148-24-3 (8-hydroxyquinoline)
Abamectin (aka avermectin)	71751-41-2
Cymoxanil	57966-95-7
Dodemorph	1593-77-7
Fluazinam	79622-59-6
Hymexazol	10004-44-1
Penconazole	66246-88-6
Sulcotrione	99105-77-8
Thiacloprid	111988-49-9
Triadimenol	55219-65-3

Table A 26 - List of active substances classified STOT RE1

Substance	CAS number
Diquat (dibromide)	2764-72-9 (ion), 85-00-7 (dibromide)
Fipronil	120068-37-3
Fluquinconazole	136426-54-5
Warfarin (aka coumaphene)	81-81-2

Table A 27 - List of active substances classified STOT RE2

Substance	CAS number
Alpha-Cypermethrin (aka alphamethrin)	67375-30-8
Amitrole (aminotriazole)	61-82-5
Chlorpropham	101-21-3
Clodinafop	114420-56-3
Diuron	330-54-1
Famoxadone	131807-57-3
Flufenacet (formerly fluthiamide)	142459-58-3
Glufosinate	77182-82-2
Ioxynil	13684-83-4
Linuron	330-55-2
Molinate	2212-67-1
Oxadiargyl	39807-15-3
Oxasulfuron	144651-06-9
Propineb	12071-83-9 (monomer), 9016-72-2 (homopolymer)
Quizalofop-P-tefuryl	119738-06-6
Thiram	137-26-8
Tri-allate	2303-17-5
Ziram	137-30-4