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SUPERSEDED GUIDANCE - NEWER VERSION AVAILABLE

Guidance on information requirements

~~GUIDANCE ON REGULATION (EU) No 528/2012 CONCERNING THE MAKING AVAILABLE ON THE MARKET AND USE OF BIOCIDAL PRODUCTS (BPR)~~

Version 1.0
July 2013

LEGAL NOTE
This document contains guidance on Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products (Biocidal Products Regulation, the BPR). This document describes the BPR obligations and how to fulfil them. However, users are reminded that the text of the BPR is the only authentic legal reference and that the information in this document does not constitute legal advice. The European Chemicals Agency does not accept any liability with regard to the contents of this document.

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Foreword

This Guidance is to be applied to applications for active substance approval and product authorisation as submitted from 1 September 2013, the date of application (DoA) of the Biocidal Product Regulation (the BPR). From the DoA, this Guidance replaces the Technical Notes for Guidance (TNsG) on Data Requirements (EU, 2008a) in support of Directive 98/8/EC (Biocidal Product Directive - BPD).

The BPR lays down rules and procedures for the approval of biocidal active substances and the authorisation of biocidal products.

Consequently, applicants should use this document when preparing dossiers according to:

- Articles 4-9 on validation, evaluation and approval of a new active substance,
- Articles 13 and 14 on the renewal of an approval,
- Articles 12-15 on the review of an approval, or
- Articles 19-21 on the authorisation of a biocidal product.

This Guidance deals with the information requirements on active substances and on biocidal products. It is based on the TNsG on data requirements under the BPD. However, the information requirements compared to the BPD have changed. Major differences are:

1. The term *information requirement* is used instead of *data requirement.* The new term reflects the fact that applicants do not, in all cases, need to supply data, i.e. information originating from studies but also general information such as addresses and names as well as (quantitative) structure–activity relationship (Q)SAR and so forth.
2. The harmonisation with Guidance from other legal frameworks was a key objective:
    a. When applicable, endpoint sections entail a reference to a relevant REACH (Regulation (EC) No 1907/2006 on Registration, Evaluation, Authorisation and Restriction of Chemicals) Guidance if available;
    b. When applicable, Guidance from the Plant Protection Products Regulation (PPPR, Regulation (EC) No 1107/2009) – Uniform Principles is referred to.
3. The structure has been modified in accordance with the new BPR Annex structure:
    a. The core data set (CDS) and additional data set (ADS) are listed in the same chapter.
    b. The specific rules for adaptation from standard information requirements (including those given by BPR Annex II and III column 3) are included in the respective endpoint sections, where available.
4. The core data requirements have been modified and certain long term animal studies are only required when necessary.
5. The BPR also allows for a more systematic approach to the adaptation of information requirements based on exposure as well as the use of techniques such as read-across, (Q)SAR and calculation methods.

6. The principle of proposing and accepting adaptations to the information requirements has been formalised and Member States have to inform and, if possible, assist the applicants with their adaptation requests.

7. It is possible to provide a reduced data package on a case-by-case basis when applying for product authorisation, taking into account the nature of the product and the expected level of exposure.

It is recognised that the Guidance document still contains gaps. So far, the main points to be addressed in future revisions or through separate Guidance documents are identified as:

- Guidance on endocrine disruption (active substance endpoint 8.13.3) and identification of endocrine activity (product endpoint 9.10); criteria for the determination of endocrine disrupting properties will not be available before 13 December 2013 according to Article 5(3) of the BPR;

- Guidance on nanomaterials is pending the ongoing review by OECD of all existing methodologies in order to identify and implement the necessary changes needed for their application to nanomaterials;

- Guidance on substances of concern and Guidance on micro-organisms are under development.

Version	Changes	Date
1.0	First edition	July 2013

Guidelines for reading this Guidance document

- Text written in *italics* originates from the BPR or its Annexes. In some specific cases, *italics* are also used to highlight special terms.

- Numbering of the requirements corresponds to the numbering in the BPR Annexes II and III.

Table of contents

List of figures

List of tables

List of abbreviations

Standard term / Abbreviation	Explanation
(Q)SAR	(Quantitative) structure activity relationship
°C	Degree(s) Celsius (centigrade)
AAS	Atomic absorption spectrometry
ADME	Administration distribution metabolism and excretion
ADI	Acceptable daily intake
ADS	Additional data set
AEL	overall systemic limit value for the human population
AI	Active ingredient
ASTM	American Society for Testing and Materials
BCF	Bioconcentration factor
BPC	Biocidal Products Committee (ECHA body)
BPD	Biocidal Products Directive. Directive 98/8/EC of the European Parliament and of the Council on the placing on the market of biocidal products
BPR	Biocidal Products Regulation. Regulation (EU) No 528/2012 of the European Parliament and of the Council concerning the making available on the market and use of biocidal products
CA	Chemical abstract
Cat	Category
CAS	Chemical abstract (Service or System)
CAS registry number	A CAS registry number (Chemical Abstract Service index number) is a unique numerical identifier for chemical compounds, polymers, biological sequences, mixtures and alloys and does not have any chemical significance
CDS	Core data set
CEFIC	European Chemical Industry Council
CEN	European Committee for Normalisation
CEPE	European Committee for Paints and Inks
CIPAC	Collaborative International Pesticides Analytic Council Ltd.
CLP (Regulation)	Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures
CO_2	Carbon dioxide
ConsExpo	The software model ConsExpo is a set of coherent, general models that enables the estimation and assessment of exposure to substances from consumer products that are used indoor and their uptake by humans.
CSR	Chemical safety report
d	Day(s)
dw	Dry weight
Doc	Document
DAD	Diode array detector
DG	European Commission Directorate General
DG SANCO	European Commission Directorate-General for Health and Consumers

Standard term / Abbreviation	Explanation
DIN (TTC,INT)	Deutsches Institut für Normung e.V. (German Institute for Standardisation)
DNA	Deoxyribonucleic acid
DNT	Developmental Neurotoxicity
DoA	Date of application
DSC	Differential Scanning Calorimetry
$DegT_{50}$	Period required for 50% degradation (define method of estimation)
$DegT_{90}$	Period required for 90% degradation (define method of estimation)
$DisT_{50}$	Period required for 50% dissipation (define method of estimation)
$DisT_{90}$	Period required for 90% dissipation (define method of estimation)
$DegT_{50lab}$	Period required for 50% degradation under laboratory conditions (define method of estimation)
$DisT_{90field}$	Period required for 90% dissipation under field conditions (define method of estimation)
DTA	Differential Thermo-Analysis
DWD	European Drinking Water Directive (Directive 98/83/EC)
EC	European Communities or European Commission
EC_{50}	Median effective concentration
EC method	Test Method as listed in the Test Methods Regulation
ECD	Electron Capture Detector
ECHA	European Chemicals Agency
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
EEC	European Economic Community
EFSA	European Food Safety Agency
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of (new or notified) Chemical Substances
EMA	European Medicines Agency
EN	European norm
EPA (DK, USA)	Environmental Protection Agency (of Denmark, or the United States of America)
EPPO/OEPP	European and Mediterranean Plant Protection Organization
ESD	Emission Scenario Document, Guidance developed under the BPD tailored for biocides
EU	European Union
EWPM	European Wood Preservation Manufacturers
FCM	Food contact material
FELS	Fish early-life stage
FID	Flame ionisation detector
f_{OC}	Organic carbon factor (compartment depending)

Standard term / Abbreviation	Explanation
FOCUS	Forum for the Coordination of Pesticide Fate Models and their Use (European pesticide project for risk assessment)
FPD	Flame photometric detector
g	Gram(s)
GC	Gas chromatography
GLP	Good laboratory practice
h	Hour(s)
ha	Hectare(s)
HLC	Henry's Law Constant
HPLC	High performance (or pressure) liquid chromatography
IC_{50}	Median immobilisation concentration or median inhibitory concentration 1 (explained by a footnote if necessary)
ICP	Inductively coupled plasma
ICP-MS	Inductively coupled plasma mass spectrometry
ICP-OES	Inductively coupled plasma optical emission spectrometry
IHCP	Institute for Health and Consumer Protection (DG Joint Research Centre)
ILV	Independent laboratory validation
INDEX number	The INDEX number (format XXX-XXX-XX-X) is a European number attributed to substances listed on Part 3 of Annex VI to CLP Regulation (List of harmonised classifications and labelling).
INT	2-p-iodophenyl-3-p-nitrophenyl-5-phenyltetrazoliumchloride testing method (please refer to DIN)
IOBC	International Organisation for Biological Control of noxious animals and plants
IR	Infrared
IPCS	The WHO International Programme on Chemical Safety
ISBN	International standard book number
ISO	International Standards Organisation
ISO (TC, SC, WG)	International Standards Organisation Technical Committee, Scientific Committee, Working Group
ISSN	International standard serial number
ITS	Integrated testing strategy
IUCLID	International Uniform Chemical Information Database
IUPAC	International Union for Pure and Applied Chemistry
JRC	Joint Research Centre
k	Kilo- or rate constant for biodegradation
K	Kelvin
Ka	Acid dissociation coefficient
Kb	Base dissociation coefficient
Kd	Desorption coefficient
kg	Kilogram(s)

Standard term / Abbreviation	Explanation
K_{oc}	Organic carbon adsorption coefficient
K_{ow}	Octanol-water partition coefficient
K_P	Solid-water partitioning coefficient of suspended matter
kPa	Kilopascal(s)
Kst	Dust explosion constant
L	Litre(s)
$L(E)C_{50}$	Lethal concentration, median
LD_{50}	Lethal dose for 50% of the group of tested animals
LEL	Lower explosion limit
LLNA	Murine local lymph node assay
LOC	Limiting oxygen concentration
log	Logarithm to the basis 10
LOQ	Limit of quantification
m	Metre
MAC	Maximum admissible concentration
mg	Milligram(s)
MIE	Minimum ignition energy
MIT	Minimum ignition temperature
MITI	Ministry of International Trade and Industry (Japan)
MMAD	Mass median aerodynamic diameter
mol	Mole(s)
MOTA	Manual of Technical Agreements of the Biocides Technical Meeting
MRL	Maximum residue limit
MS	Mass spectrometry
MSCA	Member State competent authority
MSn	A number of coupled mass spectrometers
MT	Material test
nm	Nanometre(s)
NMR	Nuclear magnetic resonance
no.	Number
NOAEC	No observed adverse effect concentration
NOAEL	No observed adverse effect level
NOEC	No observed effect concentration
NOEL	No observed effect level
NPD	Nitrogen phosphorus detector
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational exposure limit
OH	Hydroxide
OPPTS	Office of Prevention, Pesticides, and Toxic Substances (U.S.-EPA)
OSHA	European Agency for Safety and Health at Work
Pa	Pascal(s)
Para.	Paragraph
PBPK	Physiologically-based pharmaco(toxico)-kinetics
PEC	Predicted environmental concentration

Standard term / Abbreviation	Explanation
pH	pH-value, negative decadic logarithm of the hydrogen ion concentration
pKa	Negative decadic logarithm of the acid dissociation constant
pKb	Negative decadic logarithm (to the basis 10) of the base dissociation constant
PNEC	Predicted no effect concentration
PPPR	Plant Protection Products Regulation, Regulation (EC) No 1107/2009
PT	Product-type
r	Correlation coefficient
RA	Risk Assessment
RAC	Committee for Risk Assessment (ECHA body)
$rate_{a.s.}$	Use rate of active substance [kg /ha]
$rate_{metabolite}$	Application rate at which metabolite should be tested (kg/ha)
REACH	Regulation EC No 1907/2006 on Registration, Evaluation, Authorisation and Restriction of Chemicals
rf.	Refer
RIVM	Rijksinstituut voor Volksgezondheid en Milieuhygiëne (Dutch National Institute of Public Health and Environmental Protection)
RMS	Rapporteur Member State
RSD	Relative standard deviation
s	Second(s)
S/L	Short-term to long-term ratio
SCAS	Semi-continuous activated sludge (inherent biodegradability tests)
SDS	Safety data sheet
SETAC	Society of Environmental Toxicology and Chemistry
SMEs	Small and medium-sized enterprises
SMILES	Simplified molecular-input line-entry system
STP	Sewage Treatment Plant
TC	Technical material In accordance with FAO manual (FAO, 2010), TC is usually the final product from preparation of the active substance prior to being formulated into an end-use product. This may contain a stabiliser and/or anti-caking or anti-static agents (if required) but no other additives. TC is usually ≥900 g/kg with solvent(s) removed during synthesis, with only residual amounts remaining (usually ≤10%) and no solvent added subsequently.
Test Methods Regulation	Regulation (EC) No 440/2008 laying down test methods pursuant to the REACH Regulation

Standard term / Abbreviation	Explanation
TK	Technical concentrate In accordance with FAO manual (FAO, 2010), TK may also be the final product from preparation of the active substance but it may contain additives (not formulants) in addition to a stabiliser, for example as safety agents. TK may also contain solvent(s) (including water), either deliberately added to a TC or not removed during preparation.
TG	Technical guideline(s), technical group(s)
TGD	Technical Guidance Document (EU, 2003)
TM	Biocides Technical Meeting, an established subsidiary body responsible for the implementation of the Biocidal Products Directive, together with the European Commission.
TNsG	Technical Notes for Guidance
TTC	2,3,5-Triphenyltetrazoliumchloride testing method (please refer to DIN)
UDS	Unscheduled DNA synthesis
UN	United Nations
UV	Ultraviolet
UVC	Unknown or variable composition, complex reaction products
UVCB	Undefined or variable composition, complex reaction products or biological material
v/v	Volume per volume ratio
VDI	Verein Deutscher Ingenieure (The Association of German Engineers)
VIS	Visible
w/w	Weight per weight ratio
WHO	World Health Organisation
µg	Microgram(s)

I. INTRODUCTION TO THE GUIDANCE ON INFORMATION REQUIREMENTS

Regulation (EU) No 528/2012 of the European Parliament and of the Council (the BPR) lays down rules and procedures for approval of the active substances in biocidal products at Union level and for the authorisation of biocidal products in both Member States and at Union level. The objective of the BPR is to improve the functioning of the internal market on biocidal products whilst ensuring a high level of environmental and human and animal health protection. In addition, the BPR removes a number of deficiencies that were identified during the implementation of Directive 98/8/EC of the European Parliament and of the Council on the placing on the market of biocidal products (BPD).

A key ambition of the BPR is the harmonisation of information requirements. The basic rule is that study data and other information, required for the inclusion of an active substance in the *Union list of active substances approved for use in biocidal products,* are the same throughout the European Union (EU). Study data and other information must fulfil the minimum requirements whilst being sufficient to conduct a proper risk assessment in order to finally allow for a decision on the suitability of the substance to be approved or, the product to be authorised.
The BPR itself entails rules on information requirements (especially in Articles 6-8). The information requirements are specified for active substances in Annex II, and for the respective biocidal products in Annex III (in Title 1 of Annex II/III for chemicals and Title 2 of Annex II/III for micro-organisms).

Due to the wide scope of the BPR and the extensive variation of exposure and risks of biocidal products, the general rules provided in the BPR and its Annexes have to be specified in order to ensure efficient and harmonised day-to-day implementation of the regulation. The aim of the Guidance is to provide detailed and practical direction on which study data and other information should be submitted, when applying for approval and authorisation according to the BPR. The requirements outlined in sections 6 of Chapters II and III of the Guidance are also applicable for the simplified authorisation procedure, i.e. those products that fulfil all conditions of the requirements listed in Article 25 of the BPR.

It should be noted that only chemical biocidal products (Title 1 of Annex III), including treated articles, and chemical active substances (Title 1 of Annex II) are covered by the present document. Guidance on information requirements for substances of concern in the biocidal product, Guidance on micro-organisms and Guidance on nanomaterials will be available separately. Guidance on nanomaterials is pending an ongoing review by the OECD of all existing methodologies in order to identify and implement the necessary changes needed for their application to nanomaterials.

Several documents published by the Commission and ECHA have been used as a basis for the information requirements presented. The most important documents are listed in the Chapter Section 1.3.

This Guidance primarily addresses applicants, seeking approval of an active substance and for authorisation of a biocidal product, who are obliged to submit information to the evaluating Member State competent authorities. The MSCAs task is then to assess the adequacy and relevance of the submitted information.

1.1. Structure of the Guidance on information requirements

1.1.1. Information requirements

The information requirements are two-tiered:

I. The core data set (CDS) is mandatory for all product-types. This information always has to be submitted, unless the rules for adaptation of standard information are applicable (see below).

II. The additional data set (ADS) might be required to perform the risk assessment under the following conditions:

   a. ADS information on physical chemical properties, methods of detection and identification and on the toxicological profile is required depending on the intrinsic properties of the active substance or the biocidal product.

   b. ADS information on the ecotoxicological properties and the environmental fate and behaviour of the active substance or biocidal product is required depending on the product-type, i.e. the foreseen use and route of exposure.

   c. ADS information on the ecotoxicological properties and the environmental fate and behaviour might be required to refine the initial risk assessment.

The information requirements are divided into two parts:

1) The CDS and ADS for active substances in Chapter II,

2) the CDS and ADS for biocidal products in Chapter III.

The CDS together with the ADS comprise the complete set of information on the basis of which an overall and adequate risk assessment can be carried out.

1.1.2. Comparison BPD-BPR

Figure 1 represents a comparison of the structure of the data requirements or information requirements, respectively, under the BPD and under the BPR. In the BPD legal text as well as in the TNsG on data requirements (EU, 2008a), CDS and ADS are listed in separate Annexes. In contrast, the BPR text lists both CDS and ADS in the same Annexes. In addition, '*specific rules for adaptation from standard information concerning some of the information requirements that may require recourse to testing of vertebrates*' represent data waiving possibilities and are listed alongside the respective endpoints in Annexes II and III in the BPR.

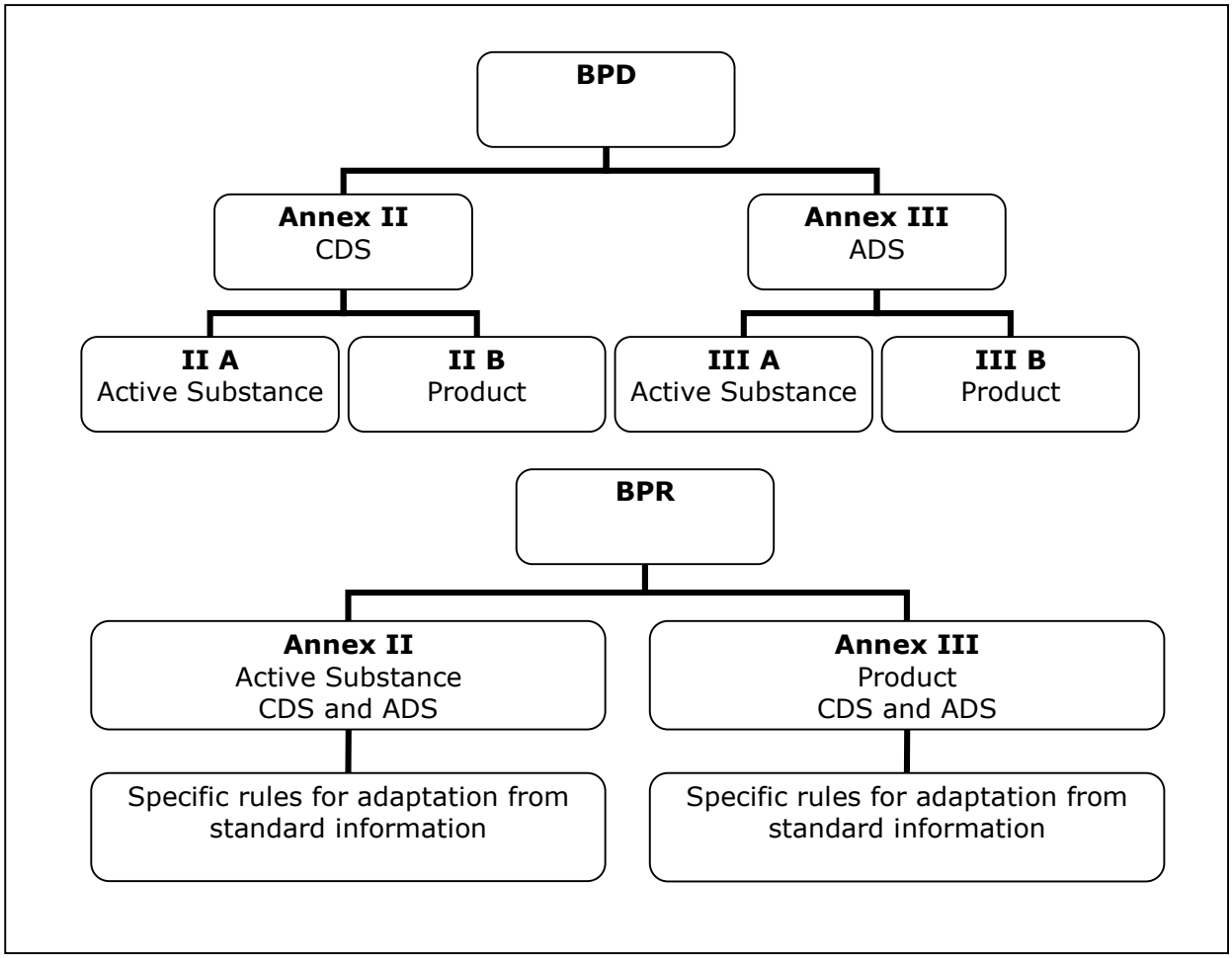

Figure 1 Structure of data/information requirements under the BPD and the BPR.

Unlike under the BPD, the information requirements in Annexes II and III of the BPR are listed in three columns: column 1 contains the actual requirements, column 2 indicates whether it is a CDS or an ADS, column 3 contains waiving statements when applicable (see Table 1). General rules for data waiving can be found in Annex IV of the BPR.

Table 1 Three-column- structure of BPR information requirements in Annexes II and III of the BPR.

COLUMN 1	COLUMN 2	COLUMN 3
Information requirement	ADS label or no label (for CDS)	Specific rules for adaptation from standard information concerning some of the information requirements that may require recourse to testing of vertebrates.

1.1.3. **Document structure**

This document consists of several chapters:
Chapter I contains general guiding principles for information submission.

Chapter II covers CDS and ADS information requirements as listed in Title 1 of Annex II of the BPR. The chapter explains the BPR requirements for active substances (chemical substances) and contains references to relevant test methods and further guidance. For example, it offers guidance on which test is the most suitable for specific cases. In addition, the chapter contains the *specific rules for adaptation from standard information*, where applicable. These *waiving* rules are generally accepted, scientifically or technically justified exemptions to the information requirements.

Chapter III provides CDS and ADS information requirements as listed in Title 1 of Annex III of the BPR. The chapter explains the BPR requirements for biocidal products (chemical products) and contains references to relevant test methods and further guidance. Similar to Chapter II, it also contains references to relevant test methods and explains the Annex III requirements. It also lists the *specific rules for adaptation from standard information*.

The endpoint-specific sections (Chapters II and III) are structured in the same way as the BPR text.

Chapter IV provides guidance on the testing strategies for biotic and abiotic degradation.

Chapter V provides guidance on the required ADS information for each of the 22 different product-types. Reflecting the environmental exposure due to the use of the different product-types, submission of that information is mandatory.

Chapter VI contains guidance for substances of concern (under development).

1.2. Guiding principles with regard to information requirements

The following guiding principles reflect the general guidance on information requirements as provided in the BPR.

1. **The common core data set (CDS)** forms the basis of the requirements. In general, it is regarded to be a **minimum set** required for all substances and product-types.

2. **The additional data set (ADS)** includes supplementary information requirements. This information may be required depending on **the characteristics** of the active substance and/or the product-type and on the expected exposure of humans, animals and the environment. The product's use or application method needs to be taken into account under both the proposed normal use and a possible realistic worst case situation (Article 19(2)).

3. **The adaptation of information requirements** (i.e. 'data waiving') outlined throughout this Guidance is possible in certain cases for both CDS and ADS. As an example, some of the toxicological information requirements may be adapted occasionally when the exposure is limited or when other product-type-specific factors apply. Sufficient and acceptable justification needs to be provided for the adaptation. In addition, the inherent physical and chemical properties of the substance or the product may justify waiving of some

information requirements. For guidance on General Rules for the Adaptation of the Data Requirements see Chapter I Section 1.5 (under development).

4. The information requirements have been specified in as much detail as possible. However, in certain cases, **expert judgement** by the applicant and by the competent authority may be necessary in order to assess, for instance, whether an additional study is needed or on which organism or under which conditions a test should be performed. The applicant should propose the initial expert judgement, which is then examined during the evaluation. In making the decision as to whether additional testing is justified, the benefit for the risk assessment, the compatibility with accepted risk assessment rationales, and the feasibility of the required tests may have to be considered. When providing an expert judgement one must, when relevant, take into account both the proposed normal use and a possible realistic worst case situation. Expert judgement decisions should be scientifically justified and transparent. In certain cases, the final decision on information requirements is made by the Biocidal Products Committee (BPC). Special attention is required in cases where there are endpoints of concern and clearly defined or standardised methods are lacking. Here, the applicant is obliged to investigate if relevant methods are applicable. New test methods are continuously being developed and it is the applicant's duty to be up-to-date with the state of science regarding test methods.

5. It is always the **applicant who is responsible** for the submission of the data. All data provided in the application must always be supported by study reports, other data or a letter of access. The information submitted by the applicant on both active substances and biocidal products, and also on substances of concern present in the biocidal product must be sufficient for conducting a risk assessment and decision-making both at EU level and on the level of the individual Member States. The applicant should consult a competent authority to which data should be submitted. This will allow for proper risk mitigation measures to be decided upon if an active substance is likely to fail the criteria for entry into the Union list of approved active substances or if a product is likely to fail the criteria to be authorised at national or Union level.

6. The data submitted by the applicant will form the basis for classification and labelling according to CLP Regulation (harmonised classification in case of active substances and self-classification in case of biocidal products). The active substances may be subject to harmonised classification for the first time or the data can be used to review a previous harmonised classification.

7. The data and test requirements should suit the individual circumstances and thus make it possible to assess the risks under a range of conditions. The following parameters should be taken into account when preparing the application for authorisation:

    a. The characteristics of the application technique,

    b. The user type (e.g. professional or non-professional users), and

    c. The environment, in which the product is intended to be used or into which the product may be released.

8. *In order to avoid animal testing,* ***testing on vertebrate animals*** *for the purposes of this Regulation shall be undertaken* ***only as a last resort****. Testing on vertebrate animals shall not be repeated for the purposes of this Regulation.* Concerning the latter, detailed rules are provided in Article 62 of the BPR. The data generated and collected under other legislative regimes, especially under Council Regulation (EU) No 544/2011, Council Regulation (EC) No 1907/2006 and Council Regulation (EC) No 1272/2008 should be used, taking into account the rules on data protection and confidentiality. Sharing of vertebrate data submitted under the BPD or BPR is mandatory.

9. For renewal of a product authorisation the applicant must submit **all relevant data required under Article 20 that it has generated since the initial authorisation**. This requirement corresponds to the obligation to submit any new data after the authorisation has been granted (Article 13(2)). This only applies to data that were generated by the applicant and not any other data that may be available. For example, if several reports on similar studies are available to the applicant they should all be submitted to allow a more sound risk assessment with, among others, assessment of inter-species variability. The additional data should be of an acceptable quality (see Annex IV, point 1 of the BPR).

10. For the evaluation of a biocidal product, the evaluating competent authority *shall take into consideration other relevant technical or scientific information which is reasonably available to them with regard to the properties of the biocidal product, its components, metabolites, or residues;* (Annex VI, point 8a of the BPR). This means that e.g. Member States and other stakeholders should also submit relevant data to the evaluating competent authority relevant data, which is reasonably available to them but which has not been available to the applicant. The applicant is not responsible for this additional information. The applicant, however, is responsible to search for data from all sources which he or she may reasonably be expected to have access to.

11. Public literature data can be used in the assessment if the following conditions are fulfilled:

    a. The data comply with the BPR Annex II, III introduction points 5-9.

    b. The identity, purity and the impurities of the substance have to be defined in the publication and to be comparable with the substance addressed in the application.

    c. The reporting of the study allows evaluation of the quality of the study.

    If conditions a-c are met the applicant can claim that adequate data is publicly available. Providing that the quality of public data fulfils the criteria, it can be used as key studies.

12. There must be at least one key study or an accepted waiving justification for each CDS endpoint given in the BPR Annexes II and III. The same applies to ADS endpoints in the BPR Annexes II and III, depending on the product-type (in the case of ecotoxicology endpoints and environmental fate and behaviour) and on intrinsic physical-chemical or toxicological properties of the substance or the product, respectively. A key study is the critical study for a certain endpoint and has to be reliable and adequate to use for the risk assessment. For criteria on the selection of key studies and further information, see TNsG

on Preparation of Dossiers and Study Evaluation (EU, 2008b). A study with a reliability indicator of 3 or 4 cannot be a key study and can be used only as supportive information.

13. When more than one adequate study is available, expert judgement should be used to decide whether mean or median values should be used instead of the result of a single key study. If there is divergent data from acceptable studies, a study summary should be provided for all these studies. The study summary of each key study must be presented in the IUCLID file.

14. It is always possible to require additional information or studies if this is considered to be necessary for a proper risk assessment and decision making. The need for additional studies may be justified either by the properties of the chemical (i.e. hazard) or by the predicted exposure. Article 8(2) states that *where it appears that additional information is necessary to carry out the evaluation, the evaluating competent authority shall ask the applicant to submit such information within a specified time limit, and shall inform the Agency accordingly.* In that case, the stop-the-clock rule is applied. Data may also be required for a **substance of concern** present in the biocidal product other than the active substance. General rules and information requirements for substances of concern are laid down in Chapter VI (under development). However, the detailed requirements are left mainly to be judged on a case-by-case basis. If the outcome of the applicant's assessment indicates a need for more data, the applicant should already consider further requirements.

15. *During the process of evaluation, applicants and the evaluating bodies shall **cooperate** in order to resolve quickly any questions on the data requirements, to identify at an early stage any additional studies required, to amend any proposed conditions for the use of the biocidal product, or to modify its nature or its composition in order to ensure full compliance with the requirements of Article 19 and of this Annex. The administrative burden, especially for SMEs, shall be kept to the minimum necessary without prejudicing the level of protection afforded to humans, animals and the environment.* (BPR Annex VI, point 11). Specifically SMEs should be allowed extensive guidance from the competent authorities in order to be able to fulfil the obligations laid down in the BPR.

16. For the approval of the active substance a specification of the active substance will need to be derived. This specification must be representative for the manufacturing process as well as for the (eco)toxicological batches tested or, in other words, the reference source would be the source for which the (eco)toxicological data submitted cover the specification. Therefore it needs to be ensured that all impurities in the proposed specification are considered in the environmental fate and (eco)toxicological studies (batches used for the environmental fate and (eco)toxicological studies may contain impurities at levels equal or higher than the proposed specifications or it can be justified why some impurities in the proposed specification are not covered by these studies).

1.3. On the use of additional Guidance documents

1.3.1. Existing biocides Guidance and other relevant documents

This Guidance replaces the TNsG on Data Requirements in support of the BPD (EU, 2008a). The remaining Guidance and other relevant documents that have been drafted to be used under the

BPD are recommended to be followed also after 1 September 2013 until the new Guidance under the BPR is made available. This BPD Guidance and relevant documents should be utilised notwithstanding the references to the BPD and without prejudice to the scientific content. The BPD Guidance and related documents consist of:

- Emission Scenario Documents (ESD) which represent the main guidance to estimate the amount of substances released into the environment.
- Technical Guidance Document (TGD) which forms the basis for the exposure- and risk assessment of both active substances and products.
- Technical Notes for Guidance (TNsG) which deal specifically with biocides and BPD implementation.
- The Manual of Technical Agreements (MOTA) which contains decisions from Biocides Technical Meetings on the technical aspects of the risk assessment (EU, 2011a). The MOTA represents a living document, which is constantly updated. Comments from the MOTA are included in this Guidance where considered appropriate.
- EU Evaluation Manual for the Authorisation of Biocidal Products (EU, 2012a).

The BPD Guidance and MOTA are accessible either from the JRC or ECHA website:

http://ihcp.jrc.ec.europa.eu/our_activities/public-health/risk_assessment_of_Biocides/guidance-documents

http://echa.europa.eu/web/guest/guidance-documents/guidance-on-biocides-legislation.

The Evaluation Manual is available at the Biocides Circa website maintained by DG ENV:

https://circabc.europa.eu/w/browse/92668ddd-fd3e-4b7e-9232-b80686747060.[1]

1.3.2. REACH Guidance

In addition, REACH Guidance represents a major guidance source. The REACH Guidance should be taken into account for the evaluation of biocides, where relevant and indicated. The use of REACH Guidance is recommended for a number of endpoints with the intention of facilitating a harmonised approach. ECHA Guidance can be obtained from the ECHA website: http://echa.europa.eu/support.

[1] This current Guidance on information requirements will in future form a part A of the scientific Guidance in support of the BPR. Parts B and C of the technical Guidance, which are under development, will provide further information on the effects, hazard and risk assessment and evaluation of the applications. Procedural aspects of the BPR will be addressed in procedural Guidance and the Commission's technical Guidance notes. For a complete overview of the Guidance under the BPR, consult the ECHA website: http://echa.europa.eu. The above mentioned documents developed under the BPD will be utilised in preparation of the parts B and part C of the scientific Guidance under the BPR. Once this BPR Guidance is available it will replace the above BPD related documents and applicants and competent authorities will be referred to the new Guidance instead. References to the BPD Guidance as well as tentative references to the new parts B of the future guidance package under the BPR have been made within this Guidance and will be updated when the new guidance becomes available.

1.3.3. CLP Guidance

In addition, the Guidance on the Application of the CLP Criteria (ECHA, 2012a) represents an additional guidance source. This guidance document is a comprehensive technical and scientific document on the application of the CLP Regulation. ECHA Guidance can be obtained from the ECHA website: http://echa.europa.eu/support.

1.4. General guidance on generating the information

If new tests are performed in order to fulfil the data requirements, the following principles have to be followed:

According to point 5 of Annex II and Annex III of the BPR, as a general principle, tests *shall be conducted according to the methods described in Commission Regulation (EC) No 440/2008*. These methods ("EC methods") are based on methods recognised and recommended by international bodies, in particular OECD. In the event of a method being inappropriate or not described, *other methods shall be used which are scientifically appropriate*. Their use needs to be justified. Recommended test methods are listed in the endpoint sections.

According to point 6 of BPR Annexes II and III, tests *'should comply with the relevant requirements of protection of laboratory animals, set out in Directive 2010/63/EU'.*

Furthermore, point 6 of BPR Annexes II and III explains that *'Tests performed should comply with… in the case of ecotoxicological and toxicological tests, good laboratory practice…. **or** other international standards recognised as being equivalent by the Commission or the Agency.'* At the moment there are no "other international standards" considered equivalent to GLP.

In addition the point 6 of BPR Annexes II and III declares that '*Tests on physico-chemical properties and safety-relevant substance data should be performed at least according to international standards*.') The test methods for the physico-chemical properties are described in the Test Methods Regulation (EC No 440/2008), whereas preferred tests for the purposes of physical hazard classification are referred to in Part 2 of Annex I to CLP Regulation, via references to the UN Recommendations on the Transport and Dangerous Goods, Manual of Test and Criteria, UN-MTC (UN, 2009). The testing according to international standards should be interpreted as testing carried out by laboratories complying with a relevant recognised standard (e.g. ISO/IEC 17025, ISO 9001).

However, most of the methods listed in the Test Methods Regulation '*are developed within the framework of the OECD programme for Testing Guidelines, and should be performed in conformity with the principles of Good Laboratory Practice, in order to ensure as wide as possible 'mutual acceptance of data'*. From 1 January 2014, new tests for physical hazards must be carried out in compliance with a relevant recognised quality system or by laboratories complying with a relevant recognised standard as stipulated by Article 8(5) of CLP Regulation. Where relevant recognised standards for testing are applicable, the use of the most recent updates is advised, for example the EN and ISO standards.

Where test data exist that have been generated before the DoA of the BPR by methods other than those laid down in the Test Methods Regulation, the adequacy of such data for the purposes of the BPR and the need to conduct new tests according to the Test Methods Regulation must be decided on a case-by-case basis. Amongst other factors, the need to minimise testing on vertebrate animals needs to be taken into account (Article 90(2) of the BPR). Such a decision should first be proposed by the applicant when collecting data for the application and then evaluated by the competent authority when checking the completeness of the application and approving the

justification provided for such a case. If a test has been performed, that does not comply with the Test Methods Regulation, the nature of the differences must be indicated and justified. The same applies to deviations from the test protocol used. The test protocol should be provided in full unless there is sufficient detail in the test report.

In certain cases, testing can be replaced by modelling using (Q)SAR, Quantitative Structure Activity Relation. ECHA Guidance on (Q)SARs and grouping of chemicals is available on the ECHA website. The TGD on risk assessment for new notified substances and existing substances (EU, 2003) contains further information.

As a general rule, tests on the active substance should be performed with the substance as manufactured. For some of the physical and chemical properties' tests, a purified form of the substance is being tested, which is indicated by footnote 2 in Annex II column 1 of the BPR, in other cases, the applicant is free to choose between testing on either purified form or the form as manufactured as indicated by footnote 1 in Annex II column 1 of the BPR. The "*Active substance as manufactured*" is the active substance in its natural state or as obtained by a production process. This includes any additive necessary to preserve the stability of the products and any impurity deriving from the process used. It excludes, however, any solvent which may be separated without affecting the stability of the substance or changing its composition. Furthermore, the identity, purity and the impurities of the substance have to be defined and to be comparable with the substance subject to the application.

In order to implement the three R's, **R**eplacement, **R**efinement and **R**eduction of animals in research, the following should be taken into account when planning new tests: If there is an established EC test method or OECD test guideline for a given purpose, for example testing of acute oral toxicity, and in addition one or more alternative methods which may equivalently be used, the test method that requires a lower number of test animals and/or causes less pain should be used. A number of alternative tests either not using test animals or reducing the number of test animals are under development and when endorsed, these tests are preferred when new tests have to be performed.

A substance listed as an active substance in the *Union list of approved active substances* should be related to the active compound in the formulation. This means that a case-by-case decision must be taken by the evaluating competent authority on what to list. This could be for example simple ions or different molecular structures, precursor/activator, or unstable/breakdown active components, or multiple component products. The specifications of the used material need to be described in detail (BPR Annex II point 7) i.e. a brief description of the composition for all batches used in tests is needed. Where testing is done using an active substance the material used should be of the same specification as that which would be used in the manufacture of preparations to be authorised except where radio labelled material is used. All batches of a substance or a product used for testing should be representative of typical commercial material for which the approval is applied for and within the production concentration range. If for any test the composition of the substance or product is different from that quoted for commercial material, full details must be provided. Certain exceptions on this general rule are provided in this Guidance. When the long term stability is in doubt, the composition should be determined before testing. Where appropriate, details of the stability of the substance in any vehicle used during testing should also be specified. For certain tests (e.g. some physico-chemical tests) there are specific requirements for purity of the active substance.

In addition, the specific guidance provided in the relevant test guidelines should always be followed. For instance, guidance on when the testing of transformation products instead of the active substance is relevant may be found in the test guidelines concerned.

Some active substances may have characteristics that impede testing or limit the methods that can be used. Substances, which are difficult to test, need special attention (OECD, 2000a). The difficulties may arise from the chemical nature of the substance (e.g. insoluble substances, metals, complex mixtures of chemicals, oxidising substances or surface active compounds (surfactants)). Further difficulties may be owing to the activity of the substance.

Where studies are conducted using an active substance produced in the laboratory or in a pilot plant production system, the studies must be repeated using the active substance as manufactured unless it can be justified that the test material used for the purposes of testing and assessment is technically equivalent. In cases of uncertainty, appropriate bridging studies must be submitted to serve as a basis for a decision on the possible need to repeat studies. The test guidelines usually include guidance on the limitations of the method or give detailed guidance on how the method should be modified when testing chemicals with specific characteristics. Separate Guidance documents may be available for specific testing situations. For instance, Guidance on intermediate compounds has been published by ECHA (ECHA, 2010a). The Guidance provided in the Technical Guidance Document concerning risk assessment of new and existing substances Part II (EU, 2003) should also be followed when designing the testing strategy for substances that are difficult to test.

The test results must be reported properly and according to the guidelines used. The study summaries and full study reports of all key studies should be included in the data forwarded to the competent authority. Relevant analytical raw data should be provided on request. For example, individual data points should be provided in addition to mean values and calibration equations should be provided to allow a suitable evaluation of the study by an assessor.

1.5. Guidance on non-submission of information

The guidance text to be provided in this section is under development and will be made available later on. Until then please refer to Chapter 1 Section 1.4 of the TNsG on Data Requirements (EU, 2008a).

1.6. Testing of metabolites and transformation products

For the toxicology aspects of metabolites and transformation products, the possibility of the formation of metabolites not investigated by the usual testing must be taken into account. See Chapter II Section 8.8 on metabolism studies in mammals.

For environmental aspects, metabolites relevant for the risk assessment can be distinguished as:

- Major metabolite:
  - formed in amounts of ≥ 10% of the active substance at any time of the degradation studies under consideration, or
  - the metabolite appears at two consecutive sampling points at amounts ≥ 5%, or
  - at the end of the study the maximum of formation is not yet reached but accounts for ≥ 5% of the active substance at the final time point;
- Minor metabolite: all metabolites not meeting the above criteria;
- Ecotoxicologically relevant metabolite: any minor or major metabolite which e.g. poses a comparable or higher hazard than the active substance.

In general, an environmental risk assessment for the relevant compartments needs to be performed for all major metabolites. However, as a first step a semi-quantative assessment of these metabolites using the available data and expert judgement to fill data gaps may be sufficient. A quantitative assessment should be performed on a case-by-case basis.

If there is any reason for concern, a risk assessment also needs to be performed for those ecotoxicologically relevant metabolites which are minor metabolites.

1.7. Background documents

Legal texts

For the detailed legal texts (plus amendments and annexes, when applicable) cited in this guidance document and listed below in this section, please visit the eur-lex bibliographic website: http://eur-lex.europa.eu.

Regulations

Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC*; (REACH)*

Council Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH); (Test Methods Regulation)

Regulation (EC) No 1272/2008 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; (CLP Regulation).

Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC; (PPPR).

Commission Regulation (EU) No 1152/2010 of 8 December 2010 amending, for the purpose of its adaptation to technical progress, Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food.

Commission Regulation (EU) No 544/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the data requirements for active substances.

Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products; (BPR).

Commission Regulation (EU) No 487/2013 of 8 May 2013 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures.

Directives

Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances; (DSD, Dangerous Substances Directive).

Council Directive 75/440/EEC of 16 June 1975 concerning the quality required of surface water intended for the abstraction of drinking water in the Member States.

Council Directive 80/68/EEC of 17 December 1979 on the protection of groundwater against pollution caused by certain dangerous substances.

Council Directive 88/379/EEC of 7 June 1988 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations.

Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing of biocidal products on the market; (BPD).

Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption; (The Drinking Water Directive (DWD)). Consolidated version 2009-08-07.

Directive 1999/45/EC of the European Parliament and of the Council of 31 May 1999 concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations; (DPD, Dangerous Preparations Directive).

Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy; (The EU Water Framework Directive, WFD). Consolidated version 2009-06-25.

Directive 2004/9/EC of the European Parliament and of the Council of 11 February 2004 on the inspection and verification of good laboratory practice; (GLP).

Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances; (GLP).

Directive 2006/118/EC of the European Parliament and of the Council of 12 December 2006 on the protection of groundwater against pollution and deterioration; The Groundwater Directive.

Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on environmental quality standards in the field of water policy, amending and subsequently repealing Council Directives 82/176/EEC, 83/513/EEC, 84/156/EEC, 84/491/EEC, 86/280/EEC and amending Directive 2000/60/EC of the European Parliament and of the Council; The Priority Substances Directive.

Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.

Decisions

2000/532/EC: Commission Decision of 3 May 2000 replacing Decision 94/3/EC establishing a list of wastes pursuant to Article 1(a) of Council Directive 75/442/EEC on waste and Council Decision 94/904/EC establishing a list of hazardous waste pursuant to Article 1(4) of Council Directive 91/689/EEC on hazardous waste.

1.8. Sources of test methods and standards

The EC methods are published in the Official Journal of the European Union. The testing methods are described in the Test Methods Regulation (Regulation (EC) No 440/2008). They are regularly updated with new methods introduced as required. More information on the Test Methods Regulation and alternative methods is available at the website of the DG-JRC Institute for Health and Consumer Protection (http://ihcp.jrc.ec.europa.eu/our_activities/alt-animal-testing/test_method_reg).

The OECD test methods can be obtained directly via their internet address (http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals_chem_guide_pkg-en). The CIPAC methods may be purchased from the Collaborative International Pesticides Analytical Council (http://www.cipac.org).

ASTM Standards may be obtained from the American Society of Testing Methods, West Conshohocken, Pennsylvania, USA (http://www.astm.org).

European Standards (CEN standards), transposed as national standards, can be purchased from National Members and Affiliates of the European Committee for Standardisation (CEN). Contact information for CEN National Members and also draft European Standards may be obtained from the CEN Central Secretariat, Brussels, Belgium (http://www.cen.eu).

DIN Standards can be purchased from the website of DIN, the German Institute for Standardisation (http://www.din.de).

VDI Guidelines can be obtained from the website of VDI, The Association of German Engineers (http://www.vdi.de).

EPPO Guidelines may be obtained from the Secretary of the European and Mediterranean Plant Protection Organisation (EPPO), Paris, France (http://www.eppo.int/).

Orders for ISO International Standards should be addressed to the ISO member bodies (non-USA users, if subscribing to Internet from a USA-based provider, should consult the ISO member list for ordering ISO standards in their country) which are normally the primary ISO sales agents, or for customers in countries where there is no member body, to the ISO Central Secretariat, Geneva, Switzerland (http://www.iso.org/iso/store.htm).

The US EPA Office of Prevention, Pesticides, and Toxic Substances Test Guidelines can be obtained from the EPA website (http://www.epa.gov/ocspp/pubs/frs/home/testmeth.htm).

II. DOSSIER REQUIREMENTS ACTIVE SUBSTANCE

1. Applicant

1.1. Name and address

Name and address of the natural or legal entity of the applicant. If the applicant is a consortium; the composition of the consortium is required.

1.2. Contact person

Names, address, telephone and fax numbers, email, and other contact information of the applicant. If the applicant is a consortium; the information on the contact person for each member of the consortium is required.

1.3. Active substance manufacturer (name, address and location of manufacturing plant(s))

Name and address of the manufacturer(s).
Name, address and location of manufacturing plant(s).

2. Identity of the active substance

The information must be sufficient to identify the substance, to define it in terms of its specification and to characterise it in terms of its nature. The information submitted should, in any case, be sufficient to support a risk assessment demonstrating that the criteria referred to in BPR Article 4(1) are met. BPR Article 3(1)(c) defines 'active substance' *as a substance or a micro-organism that has an action on or against harmful organisms*.

2.1. Common name proposed or accepted by ISO and synonyms

The name of the active substance must be provided as registered in the list in Part 3 of Annex VI to CLP Regulation or, if the name is not included therein, as given in EINECS (the European Inventory of Existing Commercial chemical Substances) or in ELINCS (European List of New - or Notified- Chemical Substances) and the ISO common name of the substance, if available.

ECHA's classification and labelling inventory database may be used as a source for (common) names.

Generally known names, trade names, abbreviations, etc. must be included.

2.2. Chemical name (IUPAC and CA nomenclature or other international chemical name(s))

The chemical name must be provided according to IUPAC nomenclature and CAS nomenclature, if different.

For substances that may exist as isomers, each isomer, if scientifically applicable, should be given correct designation.

For substances of unknown, variable composition, or biological origin (UVCB), identity and the proportion of compounds in the reaction mixture should be provided. As the chemical composition

alone is insufficient for substance identification, the substance should in general be identified by its name, which will be generated by stating the origin or source of the starting materials and the most relevant steps taken during processing.

Further Guidance:

- ECHA Guidance for identification and naming of substances under REACH and CLP, Chapter 4, (ECHA, 2012b)

2.3. Manufacturer's development code number(s)

Company(ies) code number(s) or internal name(s).

2.4. CAS number plus EC, INDEX and CIPAC numbers

The CAS number, EC number, INDEX and CIPAC number must be provided, if available.
For mixtures of isomers the CAS and/or EC numbers of the mixture and individual isomers should be provided, if available.

The CIPAC code number system is an approach for an unambiguous coding of active ingredients and variants used for pesticides.

2.5. Molecular and structural formula (including SMILES notation, if available and appropriate)

The molecular formula should be provided according to the traditional Hill system and, where different, according to the CAS system. In addition, the SMILES notation should be provided, if available and appropriate.

An empirical formula should be determined for substances of undefined or variable composition, if possible.

For polymers the number average molecular weight (M_n) and the molecular weight distribution are required.

Further Guidance:

- ECHA Guidance for identification and naming of substances under REACH and CLP, Chapter 4, (ECHA, 2012b).

2.6. Information on optical activity and full details of any isomeric composition (if applicable and appropriate)

If the active substance is optically active the value for the specific rotation (in degrees) has to be specified, indicating the temperature of measurement (in °C) and the wavelength of the incident light source (nm). The direction of rotation should also be specified as either + or -. If a sample solution is used, the concentration and solvent name should also be provided.

Typically, specific rotation is specified as follows:

$$[\alpha]_{\lambda}^{T}$$

Where:

[α] specific rotation [°],
T temperature [°C],
λ wavelength [nm]

Full details of any isomeric composition must be included, i.e. the maximum content of the active isomer and the ratio of the content of isomers/ diastereoisomers, where relevant. All stereoisomers have to be determined using an appropriate analytical method.

Further Guidance:

- ECHA Guidance for identification and naming of substances under REACH and CLP, Appendix II (7), (ECHA, 2012b)

2.7. Molar mass

The molar mass (g/mol) must be provided.
For polymers the number average molar mass and the molar mass distribution are required.

2.8. Method of manufacture (synthesis pathway) of active substance including information on starting materials and solvents including suppliers, specifications and commercial availability

A description of the synthesis pathway in brief terms; the chemical reactions taking place, initial products, solvents and substances generated in the synthesis etc. must be presented.

For all starting materials and solvents, information on supplier, chemical specifications (e.g. SDS sheets that would indicate a basic set of information.) and commercial availability are required. The methods of extraction and purification should be provided, where relevant.

When relevant, where the data refers to a pilot plant production system, the information required must be resubmitted once the industrial scale production plant enters into operation and production has stabilised.

Chemical engineering data is not required as a rule, but submission may be required, where necessary (e.g. information on the temperatures and pressure at which synthesis takes place if not ambient and atmospheric while at such conditions dioxins could be formed).

2.9. Specification of purity of the active substance as manufactured in g/kg, g/l or %w/w (v/v) as appropriate, providing inclusively the upper and lower limit

Give typical concentration and upper and lower limits for typical commercial batches of the active substance in g/kg or %w/w.

For substances of undefined or variable composition the purity is 100% minus unreacted starting materials.

The specification should be for the active as manufactured. Where the active is delivered in a solvent and/or stabilisers are present then an explanation should be provided e.g. the active is not stable in isolation as a dry technical material (TC), the active is delivered in a solvent for ease of manufacture (including manufacture of the biocidal product), transportation, or for classification purposes etc.

An explanation as to how the specification has been derived must be provided e.g. based on the mean ± 3 standard deviation.

Where the active is manufactured as a technical concentrate (TK) then as well as a specification for the active as manufactured, a dry weight specification must be provided. The dry weight specification can be determined by calculation.

If the specification relates to the batch analysis data from a pilot plant then an updated specification based on the batch analysis data from full scale industrial production must be provided when this is available (see Chapter II Section 2.11).

2.10. The identity of any impurities and additives including by-products of synthesis, optical isomers, degradation products (if the substance is unstable) un-reacted and end-groups etc. of polymers and un-reacted starting materials of UVC-substances

The following information on impurities[2] and additives, including by-products of synthesis, optical isomers, degradation products (if the substance is unstable), unreacted and end-groups etc. of polymers and unreacted starting materials of UVC substances (biological material implied in addition by the acronym UVCB will be dealt with in the Guidance on information requirements for micro-organisms), must be provided, where possible:

- Common name and chemical name in conformity with Chapter II Sections 2.1 and 2.2,
- CAS and EC numbers, if available,
- Molecular and structural formula, conform with Chapter II Section 2.5,
- Molar mass, conform with Chapter II Section 2.7,
- The typical concentration and the range of concentrations expressed as g/kg or percentage w/w. Details of how the specification has been derived (e.g. based on the mean ± 3 standard deviations) must be provided. This should be for the active as manufactured. Where the active is manufactured as a technical concentrate (TK) then a dry weight specification must be provided as well as a specification for the active as manufactured. The dry weight specification can be determined by calculation.

[2] An impurity is an unintended constituent present in a substance as manufactured. It may originate from the starting materials or be the result of secondary or incomplete reactions during the production process. While it is present in the final substance it was not intentionally added. An impurity is regarded as significant if it occurs or potentially occurs in a quantity ≥ 1 g/kg in the substance as manufactured. A significant impurity may be considered relevant or non-relevant depending, in particular, on its known toxicological and ecotoxicological properties. An impurity can be considered of toxicological and/or ecotoxicological relevance. An impurity may be relevant even if it occurs in a quantity < 1 g/kg (e.g. very toxic substances like dioxin). Relevant impurities can be defined as substances, including but not limited to, that meet the criteria to be classified as hazardous in accordance with CLP Regulation, or the available information (e.g. from (Q)SARs) indicates that the impurity has an (eco)toxicological hazard. Relevant impurities have the inherent capacity to cause unacceptable effects within the meaning of Article 19(1)(b) of the BPR. Compared to the active substance, relevant impurities show additional (or more severe) toxic properties (in the sense of the definition above).

- The maximum content of the active isomer and the ratio of the content of isomers/ diastereoisomers, where relevant.
- An indication of the functions of the components added to the active substance prior to the formulation of the biocidal product (e.g. stabiliser, antifreeze, antifoaming agent, dispersing agent, and inhibitors) must be provided.
- If the specification relates to the batch analysis data from a pilot plant then an updated specification based on the batch analysis data from full scale industrial production must be provided when this is available (see Chapter II Section 2.11).
- Substances present in quantities ≥1 g/kg must be identified.
- Substances that are regarded as (eco)toxicologically relevant even at levels below 1 g/kg must be determined and identified.
- The limit of 1 g/kg applies to a dry technical material (TC) and therefore for technical concentrates (TK) the limit will apply to theoretical dry material. Hence impurities, even if below this limit for the TK, must be determined if they are ≥ 1 g/kg on a dry weight basis.

2.11. Analytical profile of at least five representative batches (g/kg active substance) including information on content of the impurities referred to in section 2.10.

For all active substances as manufactured, an analysis of at least five representative production batches is required. The analysis is one of the tools used to estimate whether the proposed specification of the active substance can be accepted as well as characterising the active substance in detail, in order to facilitate the risk assessment.

Where the active substance is not isolated but manufactured as a technical concentrate (TK), the batch data on the technical concentrate should be provided (i.e. on the active as manufactured). For TK a specification for the active as manufactured (TK) and a theoretical dry weight specification must be provided.

Where the active substance is generated *in situ* then batch analysis data on the precursors used to generate the active substance may be required.

General requirements

- The report must be GLP compliant.
- Data on the production date and size of the batches must be reported.
- It must be reported if the data come from pilot plant production or full scale industrial product.
- Batch analysis must be performed on batches representative of the manufacturing process for each source (manufacturing plant) being specified.
- The purity and impurity contents must be expressed in g/kg or percentage w/w.
- The analytical closure of the individual batches should be at least 98%; meaning, at least 98% of the manufactured substance should be accounted for. Only fully identified impurities may be counted towards this total (excluding e.g. sulfated ash, volatiles, insolubles etc).

- All impurities present ≥1 g/kg must be fully quantified using a validated method of analysis. The limit of 1 g/kg applies to a dry technical material (TC) and therefore for technical concentrates (TK) the limit will apply to theoretical dry material. Hence impurities, even if below this limit for the TK, must be determined if they are ≥ 1 g/kg on a dry weight basis.
- Analytical methods used must be reported in detail and should be highly specific or specific[3]. Details of the validation data requirements are outlined in Chapter II Section 5.
- Isomeric ratios of substances with chiral atoms must be investigated.
- If the possibility exists that exceptionally dangerous substances (e.g., dioxins, nitrosamines or other dangerous substances) can be formed during manufacture, these must be investigated independent of their content (even below 1 g/kg) and categorised as relevant impurities or substances of concern.
- If the presence of heavy metals is expected (e.g. for inorganic compounds), data on the content of lead, arsenic, cadmium and, if relevant, of other heavy metals is required.
- In general, batches tested should be no older than five years from the date of dossier submission. Deviation is possible if the applicant can ensure the manufacturing process has not changed.
- Where the data have been provided for pilot plant material then batch analysis data for at least five representative batches must be provided once full scale production commences.

Exceptions
If a specific or highly specific analytical method is not feasible, the applicant may use a suitable non-specific method, e.g. for the determination of peroxide contents. Confirmation of identity may be required (e.g. using mass spectral data, NMR, analysis using a different technique).

If a CIPAC method is used for quantification then, provided it has been established that the method is suitable for the substance and matrix, validation data and confirmation of identity do not need to be addressed. Example chromatograms to demonstrate the specificity of the method, where relevant, should be provided.

For active substances and precursors that cannot be defined in detail (e.g. paraffin oils, plant extracts and other complex mixtures), other means of characterisation may be used if appropriate. Marker compounds may be chosen and/or relevant physical properties may be used (e.g. diffraction index, density).

2.12. The origin of the natural active substance or the precursor(s) of the active substance, e.g. an extract of a flower

The scientific names of species, common names and strains, and polymer starting materials should be provided, if relevant.

[3] Non-specific method: Any analytical method in which quantification is based on a functional group (moiety) within the analyte rather than for the specific analyte.
Specific method: HPLC or GC method with a retention match with a reference standard of the analyte.
Highly specific method: LC-MS/MS with two ion transitions validated or GC-MS or LC-MS with three ion transitions validated and a retention time match with a reference standard of the analyte.

Further Guidance:

- Guidance to Member States and industry on the data requirements for naturally occurring substances used as attractants / repellents (EU, 2005a)
- Addendum to TNsG on Data Requirements for oils and extracts (PT 19) (EU, 2011b)

3. Physical and chemical properties of the active substance

When assessing physico-chemical properties, priority is given to first hand experimental results (primary references) provided that the methods are suitable for the substance under investigation and that they operate within their validity range. In exceptional cases, it is acceptable to use reference book data for physico-chemical properties of organic or inorganic substances. However, data on physico-chemical properties should be of sufficient quality i.e. they must be reliable.

Instead of verbal descriptions, an actual numeric value or a range should be used in the report, avoiding verbal terms such as "high" or "low" as far as possible. An exception exists for volatility. Note that some of the data generated in this section affect the classification and labelling.

For UVCB substances, some tests are scientifically not reasonable. Therefore either a justification for not providing an experimental result should be given instead. Further, a range of values, a representative value or values of the individual components should be given instead of a single value depending on the substance. For some of the endpoints, more specific Guidance regarding UVCB substances is given in the ECHA Guidance on information requirements and chemical safety assessment (ECHA, 2012c)).

Further Guidance:

- ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance, R.7.1 Physicochemical properties (ECHA, 2012c)

3.1. Appearance

3.1.1. Physical state (at 20 °C and 101.3 kPa)

In contrast to what is stated in Annex II of the BPR, the information should be provided in item 3.1.1 on the physical state (at 20 °C and 101.3 kPa).

The information provided should be for the purified active substance of a stated specification or for the active substance as manufactured, if different.

The physical state should be stated for an ambient temperature of 20 °C (293 K) and an ambient atmospheric pressure of 101.3 kPa (1 bar). The physical state may be solid, liquid, or gaseous. In addition, a substance may be a colloid, i.e. it is microscopically dispersed evenly throughout another substance in a system consisting of two separate phases. Colloids or colloidal systems may also be solid, liquid, or gaseous.

Further Guidance:

- ECHA Guidance on the Application of the CLP Criteria, Chapter 2.1.4 Physical state, (ECHA, 2012a)

3.1.2. Aggregate state (at 20 °C and 101.3 kPa)

In contrast to what is stated in Annex II of the BPR, the information should be provided in the item 3.1.2 on the aggregate state (at 20 °C and 101.3 kPa).

The information provided should be for the purified active substance of a stated specification or for the active substance as manufactured, if different.

A description of the form or structure must be reported, at an ambient temperature of 20 °C (293 K) and an ambient atmospheric pressure of 101.3 kPa (1 bar).

This can be aerosol, compact, crystalline, dispersion, fibre, filament, flakes, particulates, paste, pellets, powder, suspension, viscous, or other.

3.1.3. Colour (at 20 °C and 101.3 kPa)

The information provided should be for the purified active substance of a stated specification or for the active substance as manufactured, if different.

The colour must be reported, at an ambient temperature of 20 °C (293 K) and an ambient atmospheric pressure of 101.3 kPa (1 bar).

3.1.4. Odour (at 20 °C and 101.3 kPa)

The information provided should be for the purified active substance of a stated specification or for the active substance as manufactured, if different.

A description of the odour associated with the active substance as manufactured and of a purified active substance as noted during the handling of the materials in laboratories or production plants, must be reported, at an ambient temperature of 20 °C (293 K) and an ambient atmospheric pressure of 101.3 kPa (1 bar).

This can be e.g. ammonia-like, biting, characteristic of sulphur-containing compounds, characteristic of aromatic compounds, faint, garlic-like, odourless, pungent, slight, sweetish or other.

Odour should not be investigated for substances that are hazardous by inhalation.

3.2. Melting/freezing point

The information provided should be for the purified active substance of stated specification.

The measurement of the melting/freezing point should be taken up to 360 °C.

Usually the freezing point of liquid substances should be determined if above –20 °C. An indication that no freezing has occurred during preliminary tests is also acceptable. For viscous liquids the pour point is an acceptable alternative.

Test according to EC method A.1 (Melting/Freezing Temperature). It is advisable to use the Differential Scanning Calorimetry (DSC) or Differential Thermo-Analysis (DTA) (discussed in EC method A.1) since they give additional information about the thermal stability of the substance such as decomposition onset and energy.

If the melting/freezing point cannot be determined, the sublimation or decomposition temperature should be provided.

Further Guidance:

- ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance, R.7.1.2 Melting point/freezing point, (ECHA, 2012c)

3.3. Acidity, alkalinity

For active substances containing water, the pH of the active substance itself should be determined. If the solid and non-aqueous liquid active substances are to be used in biocidal products applied as aqueous dilutions, pH of a 1% aqueous dilution, emulsion or dispersion of the active substance should be determined. Test according to CIPAC method MT 75.3.

In cases where substances are acidic (pH<4) or alkaline (pH>10), test the acidity/alkalinity according to CIPAC method MT 31. Alternatively, test according to CIPAC method MT 191. Test according to the OECD Test Guideline 'Determination of pH, Acidity and Alkalinity' which is currently being developed.

Further Guidance:

- ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance, R.7.1.17 Dissociation Constant, (ECHA, 2012c)

3.4. Boiling point

The information provided should be for the purified active substance of stated specification.

The measurement of the boiling point should be taken up to 360 °C.

The boiling point should be measured at the normal atmospheric pressure of 101.3 kPa (1 bar) unless decomposition occurs, in which case reduced pressure can be used.

If the boiling point cannot be determined, the sublimation or decomposition temperature should be provided.

Test according to EC method A.2 (Boiling Temperature). DSC (discussed in EC method A.2) allows the determination of the melting and boiling point in a single test.

Further Guidance:

- ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance, R.7.1.3 Boiling point, (ECHA, 2012c)

3.5. Relative Density

The information provided should be for the purified active substance of stated specification.

The relative density of gas substances can be calculated from their molecular weight and the Ideal Gas Law. Polymer density should be determined by buoyancy methods, where appropriate.

For liquids and solids, test according to EC method A.3 (Relative Density), based on OECD Test Guideline 109 (Density of Liquids and Solids), which was revised in October 2012.

Further Guidance:

- ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance, R.7.1.4 Relative Density, (ECHA, 2012c)

3.6. Absorption spectra data (UV/Vis, IR, NMR) and a mass spectrum, molar extinction at relevant wavelengths, where relevant

The information provided should be for the purified active substance of stated specification.

Absorption spectra and mass spectrum must be determined and reported for the identification of impurities of concern, too.

For the UV/Vis (ultraviolet-visible spectral region), the spectra in neutral (pH = 7), acid (pH < 2) and alkaline (pH > 10) environments are required. The spectrum should be recorded in the range 200 – 400 nm for UV active substances and from 200 – 800 nm for substances which absorb in the Vis range. In addition, the molar absorption coefficient (ε) needs to be determined.

The relevant OECD Test Guideline is guideline 101 (UV-VIS Absorption Spectra).

Full interpretation of the data to support the structure is required.

Further Guidance:

- ECHA Guidance for identification and naming of substances under REACH and CLP, 4.2.1.3 Analytical Information, (ECHA, 2012b)
- Manual of decisions for implementation of the sixth and seventh amendments to Directive 67/548/EEC on dangerous substances (Directives 79/831/EEC and 92/32/EEC), 9.6 Guidance on spectral analysis (EU, 2006)

3.7. Vapour pressure

The information provided should be for the purified active substance of stated specification.

Vapour pressure at two temperatures (at 20 °C and 25 °C) or as a vapour pressure curve should be studied. The unit is the Pascal (Pa).

Where the vapour pressure is less than 10^{-5} Pa, the vapour pressure at 20 °C and 25 °C may be estimated by a vapour pressure curve.

The vapour pressure does not need to be measured, if calculations indicate that the value is significantly less than 10^{-5} Pa.

The study does not need to be conducted if the melting point is above 300 °C. A limit value based on measurement or a recognised calculation method is sufficient where the melting point is between 300 °C and 200 °C.

Test according to EC method A.4 (Vapour Pressure), based on OECD Test Guideline 104 (Vapour Pressure).

Further Guidance:

- ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance, R.7.1.5 Vapour pressure, (ECHA, 2012c)

3.7.1. Henry's law constant

The Henry's law constant (HLC) *must always be stated for solids and liquids if it can be calculated.*

The HLC depends on the water solubility, vapour pressure and molecular weight of a substance, and expresses the tendency of a substance to evaporate from aqueous solutions. The unit should be stated as Pa x m^3 x mol^{-1}. The water solubility and the vapour pressure used for a calculation of the HLC need to be given at the same temperature.

Further Guidance:

- ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance, Appendix R.7.1-1 Henry's law constant and evaporation rate, (ECHA, 2012c)

3.8. Surface tension

The information provided should be for the purified active substance of a stated specification.

The surface tension should be measured using an aqueous solution of sufficient concentration such that any surface activity potential is expressed; i.e. at 90% of saturation (the concentration must be quoted) to maximum concentration of 1g/l (where viscosity permits).

Inconsistencies between the water solubility result and the solubility reported should be fully addressed.

If the data demonstrate that the active substance is surface active the critical micelle concentration (CMC) needs to be determined.

Test according to EC method A.5 (Surface Tension), based on OECD Test Guideline 115 (Surface Tension of Aqueous Solutions).

Further Guidance:

- ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance, R.7.1.6 Surface tension, (ECHA, 2012c)

3.9. Water solubility

The information provided should be for the purified active substance of stated specification.

The studies must include the effect of pH (5 to 9) and temperature on solubility.

The water solubility should be determined at or near 20 °C.

The temperature dependent solubility at 10 °C and 30 °C should be reported, if temperature dependence is suspected in the solubility.

The water solubility should be determined unless the substance is hydrolytically unstable. Phrases such as "insoluble in water" are insufficient; instead a limit test should be performed so that a positive statement can be made (e.g. down to the analytical limit). For complex mixtures, a mass balance may be the only practical method. However, the extract should be compared (e.g. HPLC) with the mixture to check for differential solubility values of the components.

Where the stability of the active substance in aqueous media is such that the water solubility cannot be determined, a justification based on test data must be submitted.

Colloid and micelle formation and other possible observations must be reported.

No single method is available to cover the whole range of solubility values in water, from relatively soluble to very low soluble substances. General test guidelines (OECD Test Guideline 105 (Water Solubility); EC method A.6 (Water Solubility)) include two test methods which cover the whole range of solubility values but are not applicable to volatile substances. For metals and sparingly soluble inorganic metal compounds a specific water solubility approach (OECD Guidance Document 29 on Transformation/Dissolution of Metals and Metal Compounds in Aqueous media) was designed to measure transformation to the dissolved fraction under standard conditions.

Further Guidance:

- ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance, R.7.1.7 Water Solubility, (ECHA, 2012c)

3.10. Partition coefficient (n-octanol/water) and its pH dependency

The information provided should be for the purified substance of stated specification.

For substances which dissociate within an environmentally relevant pH range (pK_a 5-9), values for K_{ow} must be derived for the neutral form and also for the dissociated form.

Where the stability of the active substances in aqueous media is such that the partition coefficient cannot be determined, a justification based on test data must be submitted.

For those substances, which are extremely soluble in one of the phases, a limit value should be provided. If necessary, it can be based on the individual solubility values in n-octanol and water. If the test cannot be performed a calculated value along with calculation details should be provided, if relevant.

Test according to EC method A.8 (Partition Coefficient),corresponding partly to OECD Test Guideline 107 (Partition Coefficient (n-octanol/water): Shake Flask Method) and partly similar to OECD Test Guideline 117 (Partition Coefficient (n-octanol/water), HPLC Method). In addition, the OECD Test Guideline 123, Slow-stirring method, can be used to generate data for this endpoint.

Further Guidance:

- ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance, R.7.1.8 Partition coefficient, (ECHA, 2012c)

3.11. Thermal stability, identity of breakdown products

In contrast to what is stated in Annex II of the BPR, the information should be provided for the active substance as manufactured.

Data on thermal stability, namely the point of melting, sublimation or decomposition is to be identified.

If possible, thermal breakdown compounds are to be evaluated and the possibility of formation of dangerous substances is to be considered.

There is no relevant EC method. Test according to OECD Test Guideline 113 (Screening Test for Thermal Stability and Stability in Air).

Further Guidance:

- ECHA Guidance on the Application of the CLP Criteria, 2.9.3.3.1 Thermal stability tests and temperature control, (ECHA, 2012a)

3.12. Reactivity towards container material

Suitable container materials which are resistant against corrosion and do no react with the substance in question, and/or container materials that cannot be used with the substance, must be specified taking into consideration the properties of the chemicals (e.g. pH and impurities) and storage conditions (e.g. pressure and temperature).

The information can be obtained from experience in use and the chemical structure.

3.13. Dissociation constant (ADS)

The information provided should be for the purified active substance of stated specification unlike implied by the BPR.

The acid-base constant (pKa, pKb) should always be provided if it can be determined.

Test according to OECD Test Guideline 112 (Dissociation Constants in Water).

Further Guidance:

- ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance, R.7.1.17 Dissociation Constant, (ECHA, 2012c)

3.14. Granulometry

Must be determined and reported for active substances such as powders or granules.

Granulometry determines the particle size distribution. A presentation of the particle size distribution is necessary to interpret the data (e.g. in the form of a histogram of the particle size vs. mass, particles size vs. number of particles, etc).

The percentage of particles in mass with aerodynamic diameter <50 µm must be determined (see also Chapter II Section 8.7.2).

Many methods are available for particle size measurements, but none of them are applicable to the entire size range. For further information on granulometry testing, please consult the REACH guidance on information requirements and chemical safety assessment Chapter R.7 (ECHA, 2012c). The guidance provides more detailed information on the available international methods

for measuring particle size distribution. The applicant should select the most appropriate method for their substance.

Please follow more specific Guidance in Chapter III Section 3.5.6.

3.15. Viscosity (ADS)

This data is always required for liquid substances.

The viscosity should be determined at 20 °C and 40 ºC.
There is no relevant EC method. Test according to OECD Test Guideline 114 (Viscosity of Liquids) where the following determination methods are recommended:

- Capillary viscometer;
- Flowcup;
- Rotational viscometer;
- Rolling ball viscometer;
- Drawing ball viscometer.

Further Guidance:

- ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance, R.7.1.18 Viscosity, (ECHA, 2012c)

3.16. Solubility in organic solvents, including effect of temperature on solubility (ADS)

The information provided should be for the purified active substance of a stated specification.

Must be examined using at least two common solvents with different polarities.
Results should be provided as mg/l of solvent.

Test according to CIPAC method MT 181 (Solubility in Organic Solvents). The method is not suitable for substances with solubility under 10 mg/l.

3.17. Stability in organic solvents used in biocidal products and identity of relevant breakdown products (ADS)

The information provided should be for the purified active substance of a stated specification or the active substance as manufactured, if different.

The information is only required if the active substance as manufactured is delivered in an organic solvent.

Information on the stability of a test substance in a solvent is relevant, particularly when samples are to be stored. Factors affecting the rate of degradation include rates of hydrolysis, of photolysis and of oxidation. Identification of the degradation products will allow an assessment of whether they are likely to be more toxic than the parent material in subsequent ecotoxicity studies.

Further Guidance:

- ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance, R.7.1.16 Stability in organic solvent and degradation products, (ECHA, 2012c)

4. Physical hazards and respective characteristics

The physical hazards of the active substance (endpoints 4.1 to 4.16, Annex II of the BPR) correspond to the physical hazard classes included in CLP Regulation. The criteria and testing methods or standards for each of these physical hazards required in the BPR are described in the corresponding section of Part 2 of Annex I to the CLP Regulation.

For the purposes of determining whether a substance entails any of the physical hazards referred to in Part 2 of Annex I of CLP: the manufacturer, importer or downstream user must perform the tests required by the above mentioned Part 2, unless there is adequate and reliable information available (see Article 8(2) of CLP). Further to this for each relevant physical hazard a reference to the corresponding test according to UN Recommendations on the Transport and Dangerous Goods, Manual of Test and Criteria, UN-MTC (UN, 2009), starting with a UN test method name is provided.

Further information can be found in the Guidance on the Application of the CLP Criteria (ECHA, 2012a).

4.1. Explosives

Criteria for explosives are described in the section 2.1 of Annex I to the CLP Regulation.

Test according to UN Test series 1 to 3 (further test series 4 to 6 are necessary for classification) described in Part I of the UN-MTC.

Further Guidance:

- ECHA Guidance on the Application of the CLP Criteria, Section 2.2 Explosives (ECHA, 2012a)

4.2. Flammable gases

Criteria for flammable gases are described in the section 2.2[4] of Annex I to the CLP Regulation,.

Test according to ISO 10156 and EN 1839.

Further Guidance:

- ECHA Guidance on the Application of the CLP Criteria, Section 2.3 Flammable gases (ECHA, 2012a)[5]

4.3. Flammable aerosols

Criteria for flammable aerosols are described in the section 2.3[6] of Annex I to the CLP Regulation.

[4] Please note that the 4th Adaptation to Technical Progress (ATP) (Regulation (EU) No 487/2013) will ammend the criteria in Section 2.2, Annex I, CLP Regulation.

[5] Please note that guidance chapter 2.3 is currently undergoing an update according to the 4th ATP to the CLP Regulation which will amend the Section 2.2 of Annex I to CLP to include chemically unstable gases and will be renamed into "Flammable gases (including chemically unstable gases)".

Test according to 75/324/EC amended by 2008/47/EC which are harmonised with UN-MTC Section 31.

Further Guidance:

- ECHA Guidance on the Application of the CLP Criteria, Section 2.4 Flammable aerosols (ECHA, 2012a)

4.4. Oxidising gases

Criteria for oxidising gases are described in the section 2.4 of Annex I to the CLP Regulation.

Tests or calculation methods as described in ISO 10156 (Gases and gas mixtures. Determination of fire potential and oxidising ability for the selection of cylinder valve outlets) as amended should be performed.

Further Guidance:

- ECHA Guidance on the Application of the CLP Criteria, Section 2.5 Oxidising gases (ECHA, 2012a)

4.5. Gases under pressure

Criteria for gases under pressure are described in the section 2.5 of Annex I to the CLP Regulation.

Further Guidance:

- ECHA Guidance on the Application of the CLP Criteria, Section 2.6 Gases under pressure (ECHA, 2012a)

4.6. Flammable liquids

Criteria for flammable liquids are described in the section 2.6 of Annex I to the CLP Regulation.

Possible test methods for determining the flash point of flammable liquids are listed in Table 2.6.3, Section 2.6.4.4. of Annex I to CLP.

Further Guidance:

- ECHA Guidance on the Application of the CLP Criteria, Section 2.7 Flammable liquids (ECHA, 2012a)

4.7. Flammable solids

Criteria for flammable solids are described in the section 2.7 of Annex I to CLP Regulation.

Test according to UN Test N.1 as described in Section 33.2.1 of the UN-MTC.

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[6] Please note that the 4th Adaptation to Technical Progress (ATP) will ammend the criteria in Section 2.3, Annex I, CLP Regulation.

Further Guidance:
- ECHA Guidance on the Application of the CLP Criteria, 2.8 Flammable solids (ECHA, 2012a)

4.8. Self-reactive substances and mixtures

Criteria for self-reactive substances and mixtures are described in the section 2.8 of Annex I to the CLP Regulation.

Test according to the tests series A to H, as described in the Part II of the UN-MTC.

Further Guidance:
- ECHA Guidance on the Application of the CLP Criteria, Section 2.9 Self-reactive substances and mixtures (ECHA, 2012a)

4.9. Pyrophoric liquids

Criteria for pyrophoric liquids are described in the section 2.9 of Annex I to the CLP Regulation.

Test according to UN Test N.3 as described in Section 33.3.1.5 of the UN-MTC.

Further Guidance:
- ECHA Guidance on the Application of the CLP Criteria, Section 2.10 Pyrophoric liquids and solids (ECHA, 2012a)

4.10. Pyrophoric solids

Criteria for pyrophoric solids are described in the section 2.10 of Annex I to the CLP Regulation.

Test according to UN Test N.2 as described in Section 33.3.1.4 of the UN-MTC.

Further Guidance:
- ECHA Guidance on the Application of the CLP Criteria, Section 2.10 Pyrophoric liquids and solids (ECHA, 2012a)

4.11. Self-heating substances and mixtures

Criteria for self-heating substances and mixtures are described in the section 2.11 of Annex I to the CLP Regulation.

Test according to UN Test N.4 as described in Section 33.3.1.6 of the UN-MTC.

Further Guidance:
- ECHA Guidance on the Application of the CLP Criteria, Section 2.11 Self-heating substances and mixtures (ECHA, 2012a)

4.12. Substances and mixtures which in contact with water emit flammable gases

Criteria for substances and mixtures which in contact with water emit flammable gases are described in section 2.12 of Annex I to the CLP Regulation.

Test according to UN Test N.5 as described in Section 33.4.1.4 of the UN-MTC.

Further Guidance:

- ECHA Guidance on the Application of the CLP Criteria, Section 2.12 Substances and mixtures which in contact with water emit flammable gases (ECHA, 2012a)

4.13. Oxidising liquids

Criteria for oxidising liquids are described in the section 2.13 of Annex I to CLP Regulation.

Test according to UN Test O.2 as described in Section 34.4.2 of the UN-MTC.

Further Guidance:

- ECHA Guidance on the Application of the CLP Criteria, Section 2.13 Oxidising liquids and Oxidising solids (ECHA, 2012a)

4.14. Oxidising solids

Criteria for oxidising solids are described in the section 2.14 of Annex I to the CLP Regulation.
Test according to UN Test O.1[7] as described in Section 34.4.1 of the UN-MTC.

Further Guidance:

- ECHA Guidance on the Application of the CLP Criteria, Section 2.4 Oxidising gases (ECHA, 2012a)

4.15. Organic peroxides

Criteria for organic gases are described in the section 2.15 of Annex I to the CLP Regulation.

Test according to UN Test series A to H as described in Section 28 of the UN-MTC.

Further Guidance:

- ECHA Guidance on the Application of the CLP Criteria, Section 2.14 Organic peroxides (ECHA, 2012a)

[7] At the time of writing, work is in progress at the UN-level to modify Test O.1: Test for oxidising solids. This includes changing the reference substance and introducing a gravimetric method for the measurement. For further information, see document UN/SCEGHS/23/INF.17 available at the following link: http://www.unece.org/fileadmin/DAM/trans/doc/2012/dgac10c4/ST-SG-AC10-C4-2012-11e-ST-SG-AC.10-C3-2012-75e.pdf

4.16. Corrosive to metals

Criteria for corrosive to metals are described in the section 2.16 of Annex I to the CLP Regulation.

Test according to UN Test C.1 as described in Section 37.4 of the UN-MTC.

Further Guidance:

- ECHA Guidance on the Application of the CLP Criteria, Section 2.15 Corrosive to metals (ECHA, 2012a)

4.17. Additional physical indicators for hazards

4.17.1. Auto-ignition temperature (liquids and gases)

For liquids and gases, the term '**auto-ignition**' instead of 'self-ignition' is generally used. Auto-ignitability is of high importance for the assignment of temperature classes in explosion protection (i. e. ATEX in Europe) of plants and equipment.

Test according to EC method A.15, which references several national and international standards (e.g. EN 14522, etc.). The test procedure is applicable to gases, liquids and vapours which, in the presence of air, can be ignited by a hot surface.

Further Guidance:

- ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance, R.7.1.12.1 Auto-ignition, (ECHA, 2012c)

4.17.2. Relative self ignition temperature for solids

Criteria for self-heating substances are described in section 2.11 of Annex I to the CLP Regulation.

Test according to UN Test N.4 as described in Section 33.3.1.6 of the UN-MTC.

Further Guidance:

- ECHA Guidance on the Application of the CLP Criteria, Section 2.11 Self-heating substances and mixtures (ECHA, 2012a)

4.17.3. Dust explosion hazard

A dust explosion hazard is applicable to all powders and products containing, or able to produce, dust that can either ignite or explode when exposed to an ignition source when dispersed in air (relevant for particulates up to 1 mm in diameter).

Materials that cannot be oxidised are exempt from testing (e.g. most inorganic salts). If active substances are prone to dust explosions, describe measures to reduce the chance of dust explosions. Next to investigation of the relevant variables, which will indicate the chance and force of dust explosions in certain situations, it is also possible to dissolve an active substance in a carrier (e.g. water or oil), to form a technical concentrate (TK), to reduce the chance of dust formation.

Perform a screening method based on an open Hartman Tube according to VDI 2263 Part 1: VDI manual Chemical and process engineering – Volume 4: Occupational safety Part 1. IT-security for industrial automation – General mode) to determine whether a dust should be considered:

- Group A: Combustible dusts which ignite and propagate flame (explosive).
- Group B: Non-combustible dusts which do not ignite (non-explosive).

Category A substances should then be further tested. The following variables should be determined for explosive dusts:

Lower explosion limit
The lower explosion limit (LEL, expressed in $g.m^{-3}$) is defined as the minimum concentration of dust in air which can explode when exposed to an ignition source. A standardised test method is available, i.e. EN 14034 (part 3).

Explosion constant, maximum explosion pressure and minimum ignition energy
If a dust explosion hazard is expected, the dust explosion constant (K_{st}) should be determined by means of the explosion indices test (EN 14034, part 2), expressed in $bar.m.s^{-1}$, and the minimum ignition energy (MIE) by means of the method EN 13821. When determining the K_{st}, the p_{max} (maximum explosion pressure) is also determined.

Minimum ignition temperature and smouldering temperature
Explosions may also be induced by hot surfaces. Therefore, the minimum ignition temperature (MIT) and smouldering temperature should be investigated according to EN 50281.
If the applicant can motivate that no dust layers will be formed on top of electrical equipment, the MIT may be waved.

Silos and limiting oxygen concentrations
In case of storage in silos, it is advisable to investigate the Limiting Oxygen Concentration (LOC). Tests are not described in this Guidance Document, considering storage of dusty substances in silos is thought to be rare for biocides.

5. Methods of detection and identification

The applicant has to supply validated analytical methods required for the determination of the active substances (and where appropriate, for relevant degradation products, isomers and impurities of active substances and their additives), and for relevant residues thereof in/on soil, in air, in drinking and surface water, in body fluids and tissues, and in treated food or feeding stuffs. For substances, which are difficult to analyse, a description of the problems should be provided.

The objective of validating analytical methods is to demonstrate that they are suitable for their intended uses. The methods should allow the user to determine all of the analytes to fully characterise the active as manufactured and all the analytes included in the residues definitions established during evaluation. The methods should use commonly available techniques/equipment and avoid hazardous substances (e.g. carcinogenic substances like diazomethane, benzene or chloroform). Enforcement methods are required to demonstrate appropriate limits of quantification (LOQ), to be sufficiently selective, so that the interfering substances never exceed a percentage of the LOQ (see specific information outlined below under Chapter II Sections 5.1 and 5.2), and demonstrate acceptable recovery and repeatability.

Description of an analytical method
Full descriptions of validated methods must be provided. The submitted method description must include the following points:

- Definition of the analyte;
- Apparatus;

- Reagents (including purity as well as full details of standard compounds purity and associated method of determination or clear reference of origin, if commercially available);
- Analytical procedure including sample processing, extraction, clean up, derivatisation, determination (if appropriate);
- Description of calibration including the use of matrix matched standards (if appropriate);
- Procedure for the calculation of results from raw data;
- Result tables (if results are not presented in separate studies).

The following information should be offered if appropriate:

- Schematic diagram of the analytical procedure;
- Stages where an interruption of the procedure is possible;
- Hazards or precautions required;
- A statement about extraction efficiency of solvents used.

Analytical methods should use instrumentation regarded as "commonly available":

- GC detectors: FPD, NPD, ECD, FID, MS, MSn (incl. ion trap and MS/MS),
- GC columns: capillary columns,
- HPLC detectors: MS, MS/MS, FLD, UV, DAD,
- HPLC columns: reversed phase, ion-exchange, normal phase,
- AAS, ICP-MS, ICP-OES,
- further analytical techniques in certain cases.

Stability
If reference is sought with regard to the stability of the samples, the OECD Guidance document on pesticide residue analytical methods (OECD, 2007a) should be consulted.

Further Guidance:

- OECD Guidance Document on pesticide residue analytical methods, (OECD, 2007a)
- DG SANCO Guidance document on pesticide residue analytical methods, (EU, 2010a)

5.1. Analytical methods including validation parameters for the determination of active substance as manufactured and where appropriate, for relevant residues, isomers and impurities of the active substance and additives (e.g. stabilisers).

For impurities other than relevant impurities this only applies if they are present at ≥ 1g/kg.

Information on analytical methods is required concerning the determination of the active substance, isomers, impurities and residues of the starting materials and additives (e.g. stabilisers), which are of toxicological or ecotoxicological concern (i.e. which are relevant for risk assessment) or which are present in quantities ≥ 1 g/kg in the active substance as manufactured.

The following validation parameters must be addressed for the active substance, impurities and additives:

Recovery (Accuracy)
The determination of recovery for the active substance in the technical material (TC) is not required. However, for technical concentrates (TK) an assessment of accuracy in terms of recovery is required.

For impurities and additives, recovery rates should be determined at the level of the measurements i.e. for the determination of the active substance in a formulation or an impurity at a constant level, one recovery rate (measured at the stated composition) is sufficient.

For the determination of residues or impurities of varying levels the recovery rates should be determined for at least two concentration levels: one near the LOQ and one at two to three orders of magnitude higher and within the range of the calibration curve.

The following recoveries would be regarded as acceptable:

Table 2 Acceptable recovery values for residues or impurities

% active (nominal)	Mean % recovery	% impurities (nominal)	Mean % recovery
>10	98-102	>1	90-110
1-10	97-103	0.1-1	80-120
<1	95-105	<0.1	75-125
0.01-0.1	90-110		
<0.01	80-120		

Source: SANCO 3030/99 (EU, 2000a)

Repeatability
Repeatability of the determination of the active substance and impurities and additives should be addressed by the analysis of at least five independent sample solutions of the same batch of TC or TK. The repeatability for the active and the repeatability for impurities for the technical grade active substance should be compared, if available, to the modified Horwitz ratio, an inter-laboratory precision index.

Calibration
Analytical calibration should extend over a range appropriate for the lowest and highest (±20%) nominal concentration of the analyte in relevant analytical solutions. Duplicate determinations at three or more concentrations or single determinations at five or more concentrations should be performed.

Raw data of calibration have to be provided with the studies. The equation and plot of the calibration and the correlation coefficient (R^2) must be provided.

Specificity
Fully labelled chromatograms from the analysis of the active and all impurities and additives must be provided. These should include chromatograms from the analysis of the reference standards and the technical material. An explanation must be provided for any interference which contributes more than ± 3% to the total quantity determined.

Derivatisation
For the technical grade active substance the mean yield and precision of any derivatisation step does not need to be addressed.

Confirmation of identity
Provided the analytical method used to quantify the active, impurity or additive is specific or highly specific (see Chapter II Section 2.11 for method definitions) then analysis using a confirmatory method is not required. Where a non-specific method (e.g. a titration) is used then confirmation of identity will be required. This requirement does not need to be addressed where a

CIPAC method has been used. Information on the approaches to assess confirmation of identity is outlined in Chapter II Section 5.2.

Further Guidance:

- ECHA Guidance for identification and naming of substances under REACH and CLP; Chapters 4.2.1.3. / 4.2.2.3. / 4.2.3.2. (ECHA, 2012b)

5.2. Analytical methods for monitoring purposes including recovery rates and the limits of quantification and detection for the active substance, and for residues thereof in/on the following where relevant

Analytical methods for monitoring purposes including recovery rates and the limits of quantification and detection for the active substance, and for residues thereof in soil, air, water and sediment as well as animal and human fluids and tissues need to be provided, where relevant.

Analytical methods normally have to be validated to ascertain whether the method is suitable for the purpose. It is nevertheless possible that a specific method is not fully validated but can still be concluded as acceptable for the purpose if it is a specific method with official status (e.g. published by ISO, CEN, OSHA). Some flexibility should be allowed for such situations.

The following Guidance applies to the information requirements 5.2.1 to 5.2.4:

- Methods for the analysis of parent compounds and/or metabolites of concern must be submitted.
- For each method and for each relevant representative matrix, the specificity, precision, recovery, and LOQ must be experimentally determined and reported. Information on calibration is a key validation parameter.
- In principle, the residue methods proposed should be multi-residue methods; a standard multi-residue method must be assessed and reported in terms of its suitability for residue determination. Where the residue methods proposed are not multi-residue methods, or are incompatible with such methods, an alternative method must be proposed. Where this requirement results in an excessive number of methods for individual compounds, a "common moiety method" may be acceptable.

The following validation data are required for residue monitoring methods:

Calibration
Analytical calibration should extend over a range appropriate for the lowest and highest (±20%) nominal concentration of the analyte in relevant analytical solutions. Duplicate determinations at three or more concentrations or single determinations at five or more concentrations should be performed. Raw data of calibration have to be provided with the studies. The equation and plot of the calibration and the correlation coefficient (R^2) should be provided.

Selectivity/Specifity (matrix interference)
Uncorrected recoveries and blank (control) values should be reported. Blank values in the area of analytical interest (untreated samples and procedural blanks) have to be determined from the matrices used in fortification experiments and should not be higher than 30% of the LOQ. If this is exceeded, detailed justification should be provided. Matrix effects such as peak suppression and enhancement can also occur with some techniques such as HPLC/MS-MS and GC. To check for these effects, the calibration curve generated using standards prepared in matrix extracts of an

untreated sample (matrix matched standards) should be compared with the calibration curve generated with standards in solvents.

Fully labelled chromatograms should be provided. These should cover the analysis of a standard, a fortified sample at the lowest fortification level and an unfortified (blank) sample. Two blank control samples should be analysed per matrix.

Range of acceptable recoveries
In general, the mean recovery at each fortification level and for each commodity should be in the range of 70-110%.

Precision - Repeatability (expressed as relative standard deviation)
The precision of the method in a validation study should be reported as the relative standard deviation (RSD) at each fortification level. Five determinations should be made at each fortification level. In general, the RSD should be ≤ 20% per commodity and level. Where outliers have been identified (e.g. via Dixon's or Grubb's test) and discarded, this fact, the data of the outlier and the statistical significance must be clearly indicated. A maximum of one outlier may be disregarded at each fortification level.

Where an MRL is required then fortification at this level will also be required.

Confirmatory techniques
Confirmatory methods are required to demonstrate the selectivity of the primary method for all representative sample matrices. It has to be confirmed that the primary method detects the right analyte (analyte identity) and that the analyte signal of the primary method is quantitatively correct and not affected by any other compound.

Confirmation simultaneous to primary detection
A confirmation simultaneous to the primary detection using one fragment ion in GC-MS and HPLC-MS or one transition in HPLC-MS/MS may be accomplished by one of the following approaches:

- In GC-MS, HPLC-MS, by monitoring at least two additional fragment ions (preferably m/z > 100) for low resolution system and at least one additional fragment ion for high resolution/accurate mass system
- In GC-MSn (incl. Ion Traps and MS/MS), HPLC-MS/MS, by monitoring at least one additional SRM transition

For all mass spectrometric techniques, a mass spectrum (for a single MS) or a product ion spectrum (in case of MSn) should be provided to justify the selection of the additional ions.

Confirmation by an independent analytical technique
Confirmation can also be achieved by an independent analytical method. The following are considered sufficiently independent confirmatory techniques:

- chromatographic principle different from the original method
    - e.g. HPLC instead of GC
- different stationary phase and/or mobile phase with significantly different selectivity
    - the following are not considered significantly different:
        - in GC: stationary phases of 100% dimethylsiloxane and of 95% dimethylsiloxane + 5% phenylpolysiloxane
        - in HPLC: C18- and C8-phases
- alternative detector
    - e.g. GC-MS vs. GC-ECD, HPLC-MS vs. HPLC-UV/DAD

- derivatisation, if it was not the first choice method
- high resolution/accurate mass MS
- in mass spectrometry an ionisation technique that leads to primary ions with a different m/z ratio than the primary method (e.g. ESI negative ions vs. positive ions)

It is preferred that confirmation data are generated with the same samples and extracts used for validation of the primary method.

For the CIPAC titration method, no confirmatory method is needed.

Derivatisation
For analysis of some compounds, such as those with high polarity or with poor chromatographic properties, derivatisation may be necessary. Derivatives may be prepared prior to chromatographic analysis or as part of the chromatographic procedure (pre- or post-column). The use of derivatisation methods should be fully reported and justified. The derivative should be stable and its formation reproducible. The calibration is preferably conducted using standard solutions of that derivative, unless the derivatisation step is an integral part of the detection system. If the derivative is unavailable as a reference standard it should be generated with the sample derivatisation procedure and a full justification should be submitted. The method is considered to be specific to the analyte of interest if the derivatised species is specific to that analyte.

If the standard solution of the analyte is also derivatised then for complex matrices, the mean yield and precision of the derivatisation step must be addressed by using matrix matched standards.

Independent laboratory validation studies
Independent laboratory validation (ILV) studies are necessary to perform when compliance with an MRL is required in order to demonstrate the reproducibility of the analytical method. ILV studies are generally needed for the determination of residues in plant materials and additionally for methods for the determination of residues in food of animal origin, if such methods are required.

An ILV is not required for confirmatory methods. Usually, an independent laboratory validation should be conducted with samples of the representative commodities and tissues. The sample set (number of samples and fortification levels) of the primary validation has to be applied for the ILV also.

The laboratory chosen to conduct the ILV trials must not have been involved in the method development and in its subsequent use. Provided this criterion is met, the laboratory chosen to conduct the ILV trials may be in the applicant's organisation, but must not be at the same location. If the chosen laboratory requires communication with the developers of the method to carry out the analysis, this should be reported. Any subsequent additions or modifications to the original method should also be reported.

An ILV may not be necessary if available published multi-residue methods have been validated for the representative commodities.

5.2.1. Soil

Generally, it is confirmed during evaluation, where relevant, which compounds (parent and/or metabolites) should be monitored based on the evaluation of fate and behaviour of the active substance in the environment.

The proposed LOQ must not exceed the PNEC soil, if technically possible without exceeding the general limit of 0.05 mg/kg dw.

If the active substance degrades very quickly, i.e. $DegT_{50}$ and $DegT_{90}$ values of the active substance and the relevant metabolites are lower than two and three days; respectively, analytical methods for residues in soil are not required except in the case of continuous exposure.

5.2.2. Air

If the substance is volatile (i.e. if the vapour pressure >0.01 kPa) or sprayed, or occurrence in air is otherwise probable, the respective analytical methods need to be submitted.

Relevant health based limit values or relevant exposure levels need to be taken into account when judging the suitability of the proposed LOQ.

No confirmatory methods are required for the determination of residues in air if sufficient confirmatory methods are available (sufficient validation data are available) for the determination in soil or water (EU, 2010a).

Generally, the active substance or a relevant volatile degradation product are considered to be the relevant residues in air for monitoring purposes.

Limit of quantification
In the case of analytical methods for air regarding the general population, the LOQ must be equal or lower than the concentration C which is defined as:

$$C = \frac{AEL \times 0.1 \times 60}{20} \text{ [mg/m}^3 \text{ air]}$$

Where:

0.1	safety factor
60	body weight [kg]
20	air intake [volume per day in m³]
AEL	overall systemic limit value for the human population as a whole – resembling the AOEL. The lowest AEL value available should be used.

The approach using AEL is preferred to that using the occupational exposure limit (OEL) also in the case of analytical methods for air concerning professional users.

The methods must be suitable for detecting both particle associated and gaseous residues.

5.2.3. Water (surface, drinking, etc.) and sediment

If the substance itself and any of its degradation products fall within the definition of pesticides given in Annex I of Council Directive 98/83/EC (European Drinking Water Directive, DWD); analytical methods must be submitted that allow determination of the relevant parametric values specified in the DWD with adequate reliability.

Analytical methods must be submitted, which allow monitoring of the quality of surface water and groundwater which meet the criteria stipulated by the Directive 2000/60/EC (EU Water Framework Directive).

Detection and analytical methods for surface water obtained from ponds, rivers, streams, etc. and sediment, analytical methods for marine surface water as well as marine sediment should be provided if relevant exposure can be expected.

Residue definition
Generally, it has to be confirmed during evaluation, where relevant, which compounds (parent and/or relevant metabolites) should be monitored based on the evaluation of fate and behaviour of the active substance in the environment and the toxicological and ecotoxicological potential.

Limit of quantification for drinking water
The LOQ in drinking water must be ≤0.1 µg/L (EU drinking water limit based on DWD) or the toxicologically derived standard for drinking water where this is lower than the general limit of 0.1 µg/L.

Limit of quantification for surface water
The LOQ must be below the PNEC water if technically possible.

5.2.4. Animal and human body fluids and tissues

Where an active substance is classified as toxic or very toxic, validated analytical methods must be submitted which allow determination of the active substance at the NOAEC.

Residue definition
Active substances classified as toxic or very toxic are considered to be the relevant residues in human body fluids and tissues. They must be analysed for monitoring purposes. The inclusion of metabolites may be confirmed during evaluation.

Limit of quantification
The LOQ should be set at 0.05 mg/L for body fluids and 0.1 mg/kg for tissues.

5.3. Analytical methods for monitoring purposes including recovery rates and the limit of quantification and detection for the active substance, and for residues thereof, in/on food of plant and animal origin or feeding stuffs and other products where relevant (ADS)

(not necessary if neither the active substance nor articles treated with it come into contact with food producing animals, food of plant or animal origin, or feeding stuffs).

Analytical methods for the residues of the active substance may be required for monitoring purposes in various matrices, for control of MRL compliance, for the identification of misuse and for the estimation of human and animal exposure.

These methods should be specific for the purpose, use commonly available equipment and non-hazardous chemicals. Furthermore, a confirmatory method needs to be submitted. Residue analytical methods (primary methods, confirmatory methods and ILV) must be validated according to the latest versions of Guidance for biocides or plant protection products.

Analytical methods for residues are required, presuming that the biocidal product may come into contact with food, foodstuffs and feeding stuffs. This is always the situation for product-types 3, 4, 5 and also for certain uses of other product-types. For biocides of product-type 21 residue analytical methods must be submitted for fish and shellfish. The need for residue analytical methods for other product-types depends on the assessment of the transfer of the active substance into food and feeding stuffs.

Analytical methods in food, foodstuffs and feeding stuffs are not required for naturally occurring non-toxic active substances.

The residue analytical methods must be able to determine the relevant residue of the active substance with an LOQ below the relevant action levels or MRLs. The definition of the relevant residue is based on the physical and chemical properties of the active substance, the toxicological properties as well as the metabolism in plants and livestock. Separate residue definitions for risk assessment and for monitoring purposes must be set. Therefore, the active substance and/or relevant metabolites and degradation products could be included in the residue definition. If the active substance undergoes a complex metabolism it is highly recommended to define a marker compound.

Generally, an LOQ of 0.01 mg/kg should be met. In special cases, the LOQ may need to be lower than 0.01 mg/kg (e.g. in infant formulae and follow-on formulae).

Further Guidance:

- Guidance on pre-registration of Plant Protection Products, (EU, 2000b). This Guidance is applicable for generating residue data for the estimation of consumer exposure and supporting studies on the fate and behaviour of the active substance in foodstuffs, the environment, ecotoxicology and toxicology.
- Guidance on post-registration monitoring of pesticide residues, (EU, 2010a). This Guidance explains the requirements and the assessment on residue analytical methods for monitoring of pesticides.

The following Guidance documents are intended for the use in official laboratories involved in pesticide control in food and feed:

- Guidance Document on Method Validation and Quality Control Procedures for Pesticide Residues Analysis in Food and Feed, (EU, 2011c).
- OECD Guidance Document on pesticide residue analytical methods, (OECD, 2007a).
- OECD series on emission scenario documents number 19. Complementing guideline for writing emission scenario documents: the life-cycle step "service-life" (OECD, 2008a). While the OECD document talks about emission mechanisms of substances from (solid) articles, it is highly relevant for the evaluation of biocides uses in (solid) articles.
- Guidance on information requirements and chemical safety assessment Chapter R.17: Estimation of exposure from articles (ECHA, 2012d). The Guidance is relevant for the calculation/modelling of exposure from articles during service life. It also gives valuable guidance on how to summarise release from articles accumulated in society, emitting the same substance.

6. Effectiveness against target organisms

Active substance approval requires only a minimal efficacy assessment, sufficient to show an innate level of activity for the active substance. At the same time, information on the effectiveness and intended uses of the active substance must be sufficient to permit an evaluation of the representative biocidal product and to define its conditions of use. Actual efficacy studies are required for the representative biocidal product in accordance with Chapter III Section 6. However, as these studies serve the purpose of the active substance approval, the conditions under which they may be conducted are given below.

A detailed description of the test method should be available, and all information needed for the validation of the results should be provided. A GLP certificate is not mandatory.

6.1. Function, e.g. fungicide, rodenticide, insecticide, bactericide and mode of control e.g. attracting, killing, inhibiting

6.2. Representative organism(s) to be controlled and products, organisms or objects to be protected

Please follow guidance in Chapter III Section 6.1.

6.3. Effects on representative target organism(s)

Please follow guidance in Chapter III Section 6.3.

6.4. Likely concentration at which the active substance will be used in products and, where appropriate, in treated articles

Please follow guidance in Chapter III Section 6.4.

6.5. Mode of action (including time delay)

Please follow guidance in Chapter III Section 6.5.

6.6. Efficacy data to support these claims on biocidal products

and, where label claims are made, on treated articles, including any available standard protocols, laboratory tests or field trials used including performance standards where appropriate.

Include studies to support the claims made throughout Chapter II Section 6. If more information is needed to explain the label claim (e.g. method of application) please provide this information here. Follow guidance in Chapter III Sections 6.6 and 6.7 taking into account the following remarks:

- Efficacy data are required on the active substance at the active substance approval stage. These data should be able to demonstrate that the active substance has innate activity against a representative target species. When the active substance is in general combined with other active substances in a biocidal product, the innate activity of the active substance under approval should also be addressed on its own. The data generated in connection with the efficacy testing of the representative biocidal product may be utilised in addition to the data obtained from the testing of the active substance.

- Efficacy data are also required on the representative biocidal product (accompanying the application for the approval of an active substance). These should be able to demonstrate that the active substance has the ability to produce an effect on a representative target organism when it is included in a formulated product.
- It is not necessary to demonstrate efficacy against all of the target organisms at the active substance approval stage, as additional target organisms may be added at product authorisation.
- Where the innate activity of both the active substance and representative biocidal product against the target organisms has been demonstrated, a recommendation should be made for the active substance approval. Where activity has been demonstrated for the representative biocidal product, and where those activity levels would not be high enough for a product authorisation, the applicant should be asked to defend why the levels of activity noted should be considered acceptable. Where the applicant provides an acceptable justification, approval of the active substance should still be recommended and the efficacy more fully addressed at the product authorisation stage.
- As only a minimal evaluation of efficacy takes place at the stage of active substance approval, a comprehensive efficacy evaluation should be carried out at product authorisation.
- The term "label claims" should be interpreted to include all claims made for the efficacy of the product, not just those on the product label itself.

6.7. Any known limitations on efficacy

Please follow guidance in Chapter III Section 6.8.

6.7.1. Information on the occurrence or possible occurrence of the development of resistance and appropriate management strategies

Please follow guidance in Chapter III Section 6.8.1.

6.7.2. Observations on undesirable or unintended side-effects, e.g. on beneficial and other non-target organisms

Please follow guidance in Chapter III Section 6.8.2.

7. Intended uses and exposure

7.1. Field of uses envisaged for biocidal products and, where appropriate, treated articles

Use means all operations carried out with a biocidal product, including storage, handling, mixing and application. Uses taking place outside the Union should be disregarded. Any operation carried out with a view to exporting the biocidal product or the treated article outside the Union should also be disregarded.

The intended and possibly potential use should be indicated together with the fields of use.

The information on the envisaged use should be sufficient to allow an approximate and realistic estimation of human and environmental exposure to the product or treated article, respectively under realistic worst case conditions.

Any presumptions of exposure, which give case to exposure e.g. relevant product-types should always involve further studies/estimation of human and environmental exposure.

"Uses advised against" for reasons of protection of human health or the environment should be described in an unambiguous wording. This information should be consistent with the advice given to downstream users in Section 16 of the extended safety data sheet. Other applicants still have the option to apply for the authorisation of the biocidal product for the uses advised against (see Appendix to Part F CSR Template with explanation, Chapter 2.3 Use advised against, (ECHA, 2008a)).

The following product-type-specific guidance should be followed if applicable:

- For material preservatives, the application rate and estimated life of the treated article including repair treatment should be stated.
- For material preservatives of product-types 6, 7, 9, and 10, the different use areas in which the material treated with the product is intended to be used should be indicated for these preservatives (e.g. indoors or outdoors, in cattle sheds, or in drinking water, food storage or processing, or their facilities).
- For product-type 8, the hazard classes, as defined in the standard EN 335-1 (Durability of wood and wood-based products. Definition of use classes - Part 1: General), in which wood treated with the product is intended to be used should be indicated for wood preservatives. For uses not described in this standard, such as curative or antisapstain products, see also Guidance document by the European Wood Preservation Manufacturers' Group (EWPM, 1996) describing these other use sectors.
- For product-type 21, in addition to the fields of use, specify also if the product or treated article, respectively, is intended to be used in marine environments, in brackish water and/or in fresh waters. The uses should also distinguish between for example, aqua-culture, buoys and other small static objects, sluice doors, harbour constructions, oil rigs, inlet pipes of cooling water systems, marine sensors, ships' hulls (e.g. deep sea, coastal, inland waterway vessels), etc.
- For treated articles, intended and/or potential uses which show a specific exposure pattern should be listed, even if they belong to the same product-type (e.g. use for antimicrobial treatment of underwear, use for treatment of food containers, etc.).

7.2. Product-type(s)

The intended and possibly potential product-type(s) as listed in BPR Annex V should be indicated.

7.3. Detailed description of the intended use pattern(s) including in treated articles

Provide a detailed description of the overall use patterns linked to the fields of use envisaged. This information should be sufficient to allow for an approximate but realistic estimation of human and environmental exposure to the active substance under realistic worst case conditions.

7.4. Users, e.g. industrial, trained professional, professional or general public (non-professional)

Indicate users with the help of the user categories:

- Industrial user: user involved in manufacturing, handling and/or packaging of actives or products at industrial sites;
- Trained professional: professional user using end-products outside industry with a licence;
- Professional user: professional user using end-products outside industry;
- Non-professional user: member of the general public at a workplace or at home (consumer).

Users outside the Union should be disregarded.

The following are examples of the use(r) categories: preservatives for liquid-cooling and processing systems are used by professionals, avicides and piscicides are used by professional users other than industrial, and disinfectants for water beds are mainly used by non-professionals.

7.5. Likely tonnage to be placed on the market per year and, where relevant, for the envisaged major use categories

An estimate of the quantity of the active substance placed or to be placed on the EU market by the applicant (i.e. imported or produced) per year. The quantities for biocidal use and in which product-type(s), and where relevant, for the envisaged major use categories within each product-type. The quantities for use other than as a biocide should be indicated, if available. In case of the renewal of approved active substances, tonnage data should cover the last three years. For new substances not previously marketed, production plans covering three years after authorisation should be provided.

7.6. Exposure data in conformity with Annex VI to this Regulation

The principles of the exposure assessment, as outlined in BPR Annex VI on the common principles for the evaluation of dossiers for biocidal products points 32-34, and 45 should be taken into account when assessing the exposure associated with the uses and disposal of an active substance. According to Annex VI, an exposure assessment needs to be carried out for human and environmental populations for which exposure to a biocidal product occurs or can reasonably be foreseen.

For further guidance on exposure assessment see part B of the BPR technical Guidance (BPR guidance under development).

7.6.1. Information on human exposure associated with the intended uses and disposal of the active substance

The provided information should be sufficient to allow an approximate but realistic estimation of human (occupational and consumer) exposure associated with the proposed/expected uses and disposal of an active substance. The prediction of the exposure levels should also describe a realistic worst case situation, excluding accidental exposure and abuse. Exposure levels or concentrations need to be derived based on available measured data and/or modelling.

7.6.2. Information on environmental exposure associated with the intended uses and disposal of the active substance

The provided information should be sufficient to allow an approximate but realistic estimation of environmental exposure associated with the proposed/expected uses and disposal of an active substance. The prediction of the exposure levels in all relevant environmental compartments and respective biota should also describe a realistic worst case situation, excluding accidental exposure and abuse. Exposure levels or concentrations need to be derived based on available measured data and/or modelling.

7.6.3. Information on exposure of food producing animals and food and feeding stuffs associated with the intended uses of the active substance

To estimate exposure of food producing animals follow the Guidance on Estimating Livestock Exposure to Active Substances used in Biocidal Products (TNsG on Livestock exposure), published for consultation.

7.6.4. Information on exposure from treated articles including leaching data (either laboratory studies or model data)

Articles treated with or incorporating biocidal products can lead to consumer and environmental exposure if chemical constituents of the biocidal product are released in any way from these types of articles. Exposure from treated articles during service life may in some situations be the most significant exposure to the active substance (and to substance(s) of concern in the case of product authorisation applications). Specifically, articles consisting of different types of polymers can be used in a large range of consumer applications, which makes the exposure situation very complex. The diversity of applications has consequences both for the exposure of consumers and the environment. For consumers, possible worst case exposure scenarios have to be defined. Then, applications leading to simultaneous consumer exposure within a certain timeframe have to be modelled. For the environment, emissions from uses with similar exposure patterns (e.g. down the drain, direct exposure to soil, etc.) should be summed up for the respective compartment. When treated articles are imported into the EU, the only possible way to carry out a risk assessment is by active substance evaluation. It is therefore important that the applicant for an active substance approval describes the intended or potential uses in a way as detailed as possible so that the appropriate exposure scenarios can be applied. Here it is noted that the applicant may not always have this detailed knowledge, in particular with regards to treated articles imported into the EU.

The applicant submitting an application for approval of an active substance (or for authorisation of a biocidal product to treat an article) which is intended to be used in biocidal products to treat an article must submit an exposure assessment. The assessment can be based on model calculations with well supported default values and/or measured laboratory leaching values, or based on the results of an exposure study. For several product-types, information on leaching will be required as listed in Chapter V on product-type-specific data requirements on the foreseeable route of entry into the environment based on the envisaged use.

It has to be decided on a case-by-case basis how detailed the exposure assessment has to be: i.e. whether all intended uses in treated articles need to be covered or not. Here a balance has to be found between the ability of the applicant to obtain all the relevant information to carry out a detailed exposure assessment, the requirements for the approval process and the relevance of each use in relation to the foreseen exposure.

The need for additional data needs to be judged on a case-by-case basis. The REACH Guidance on exposure assessment on treated articles (ECHA, 2012e) is very comprehensive and can be applied in many cases. The OECD Guideline document on how to write emission scenarios for the life-cycle step service life (OECD, 2008a) can also be useful .

Environment
Depending on the use, either the tonnage approach or an approach in which leaching rates are determined from the treated article is required for the calculations. If the tonnage approach is not used, information on the likely application rate must be stated for the most relevant uses and modes of application. Generally, a detailed quantitative description of the fields of use envisaged should be given to allow for a realistic worst-case estimation of environmental exposure of the active substance (or any substances of concern for applications for product authorisation). When using the tonnage approach, it may be necessary to allocate a certain percentage of the overall tonnage to certain uses if such uses have a different exposure profile. Information on the estimated service life time of the treated article and possible reapplications, if relevant, is required.

In general, a tiered approach should be followed for leaching rate determination:

- Tier 1: worst-case assumption where 100% of the active substance (and for product authorisation applications – if present in the biocidal product – the substance(s) of concern). The life time can be different and depends on the product-type and use of the treated article.
- Tier 2: validated laboratory leaching test. The uncertainty of using a laboratory test to predict environmental concentrations should be addressed by using an assessment factor.
- Tier 3: semi-field tests or field studies. The duration of the field- or semi-field study should reflect the exposure situation and enable an extrapolation to the service life of the treated article.

The service life time of an article can be different and depends on the product-type and use of the treated article. For polymers, default values for the life times of different consumer articles are given in the OECD Emission scenario document on plastic additives (OECD, 2009a). For wood preservatives, the service life time of treated timber is defined by the mode of application and the use classes (OECD, 2009b). Guidance on extrapolation of leaching rates for life time calculations can be found in the Emission Scenario Document for product-type 8 (OECD, 2000b).

For polymers, it has to be taken into account that leaching rates can vary quite significantly depending on the type of polymer (polyethylene leaches less than polyamide), the type of application (incorporation or coating) and of the use (a regularly washed textiles leaches much more than a kitchen worktop). This observation will apply for many other types of treated articles. For wood preservatives, no reliable method exists to predict the leaching rate based on physico-chemical properties and therefore leaching studies are normally required.

For some product-types like e.g. PT 1, 2, 4, 7, 9, and 10, the biocidal product is often added as a premix concentrate to a surface treatment system or a polymer. The surface treatment system or the polymer may subsequently be applied to a surface and/or incorporated into the matrix from which leaching of the active substance(s) (and possibly substances of concern) will take place. As these surfaces/matrices may have many different characteristics, it is important that the applicant submits data for the leaching behaviour of different types of surfaces/matrices which are likely to cover the worst-case leaching behaviour. The emissions during service life are considered to be diffuse emissions that usually cause exposure on a wider scale compared to local emissions. Possible environmental emissions from articles treated with the same active substance and similar exposure patterns should be summed up. Uses within the same exposure pattern can be summarised to simplify the aggregated exposure assessment.

Further Guidance:

- ECHA Guidance on information requirements and chemical safety assessment. Chapter R.17: Estimation of exposure from articles (ECHA, 2012d)
- Guidance note on leaching rate estimations for substances used in biocidal products in PT 07, 09 and 10 (EU, 2010b)
- Workshop on determination of the leaching rate from treated wood to the environment (EU, 2005b)
- OECD Test Guideline 313 Estimation of Emissions from Preservative - Treated Wood to the Environment
- OECD Series on Testing and Assessment Number 107 Preservative- treated wood to the environment: for wood held in storage after treatment and for wooden commodities that are not covered and are not in contact with ground; ENV/JM/MONO(2009)12 (OECD, 2009b)
- CEN/TS 15119-2 (2012): Durability of wood and wood-based products - Determination of emissions from preservative treated wood to the environment - Part 2: Wooden commodities exposed in Use Class 4 or 5 (in contact with the ground, fresh water or sea water) - Laboratory method
- CEN/TS 15119-1 (2008): Durability of wood and wood-based products - Determination of emissions from preservative treated wood to the environment - Part 1: Wood held in the storage yard after treatment and wooden commodities exposed in Use Class 3 (not covered, not in contact with the ground) - Laboratory method.

Human Health

In a tier 1 exposure estimation, the chemical composition of the article is used to assess whether the total amount of the active substance (or substances of concern in case of product authorisation applications) present in the article may exceed the AEL or reference value. In a tier 2 assessment, exposure estimations may be refined by data obtained in e.g. leaching tests. Such tests must be conducted in appropriate media (for example, artificial sweat, saliva, etc.). They should also be specific for the intended material (for example type of polymer), use situation (for example mouthing, wearing on the skin), consistency of the article (for example, hard, smooth or porous) and duration of exposure. It is also important to obtain leaching rates during the service life of an article because in many cases articles give a high level of exposure during the first period of use and a lower level of exposure after repeated uses.

A special case of treated articles are food contact materials, which must also undergo a dietary risk assessment (see data requirements in Annex II 8.16 and Annex III 8.8, 8.9 and 8.10). For this, the Guidance listed below is available.

In a real life situation, daily exposure to different articles treated with the same active substance may occur. Consequently, an aggregated exposure assessment may be necessary. Uses with the same exposure pattern can be summarised to simplify the aggregated exposure assessment. If an active substance is used in a large number of different consumer articles, it is likely that a consumer is exposed from multiple uses. To reflect this in an exposure assessment, it may be considered as a first step to compare the acute exposure of single characteristic uses to a chronic AEL value.

Futher Guidance:

- TNsG on Human Exposure to Biocidal Products (EU, 2007). This document contains some models for exposure scenarios from treated articles in Section 2.9. For scenarios not

covered by the available models, the general principles for secondary exposure assessment in the document should be followed in order to build scenario-specific models.

- Guidance for Food Contact Materials (Commission Regulation (EU) No 10/2011). This regulation defines test conditions for migration studies. The migration studies give amounts of substances in food or per surface area. Consumer exposure is then calculated using the migration results and assuming a 60kg person consuming 1kg of food in contact with 6.0dm^2 FCM in a day. The EFSA Note for Guidance for petitioners presenting an application for the safety assessment of a substance to be used in food contact materials prior to its authorisation (EFSA, 2008) is currently under revision and should be consulted when finished for current body weight and food intake default values. It should be noted that only plastic materials are covered by the regulation. Other materials should be assessed in line with the principles for plastic materials.
- Suitable exposure assessment models for specific scenarios available from other sources may be used for the assessment of treated articles, e.g. a generic risk assessment model for insecticide treatment of mosquito nets and their subsequent use (WHO, 2004).

8. Toxicological profile for human and animal including metabolism

Considerations before initiating testing

Before testing is initiated all available information should be scrutinised for evidence that may indicate severe effects, serious specific system or target organ toxicity (e.g. neurotoxicity or immunotoxicity), delayed effects or cumulative toxicity. Consideration should also be given to tests already performed/submitted for the purpose of other regulatory programmes. All available information on toxicity should be taken into account when choosing the dose range for a new study. If there is concern that an effect is not adequately covered by existing OECD Test Guidelines, specialised study protocols may be used. Whenever deviating from OECD Test Guidelines a justification should also be provided. These specialised study protocols should be designed on a case-by-case basis in order to enable an adequate characterisation of these hazards, including the dose-response, threshold for the toxic effect and an understanding of the nature of the toxic effects. Where a need is identified for a modification in the study protocol to cover specific needs, this will be done in consultation with the evaluating Member State.

The endpoints that need to be addressed for the purpose of the BPR are interlinked and therefore in certain cases sequential testing needs to be taken into account to decide which tests need to be performed and in which order. This is due to the impact findings from one study can have on the classification and labelling and the risk management measures, which can make the requirement for testing of other endpoints redundant.

Figure 2 shows the relationship between this section on information requirements for the toxicological profile of substances and the Hazard Assessment part of the BPR Guidance (guidance under development). For each toxicological endpoint and the respective information requirements described in the following sections steps 1 and 2 need to be considered first to conclude on the need to conduct further testing using integrated testing strategies (ITS) where relevant.

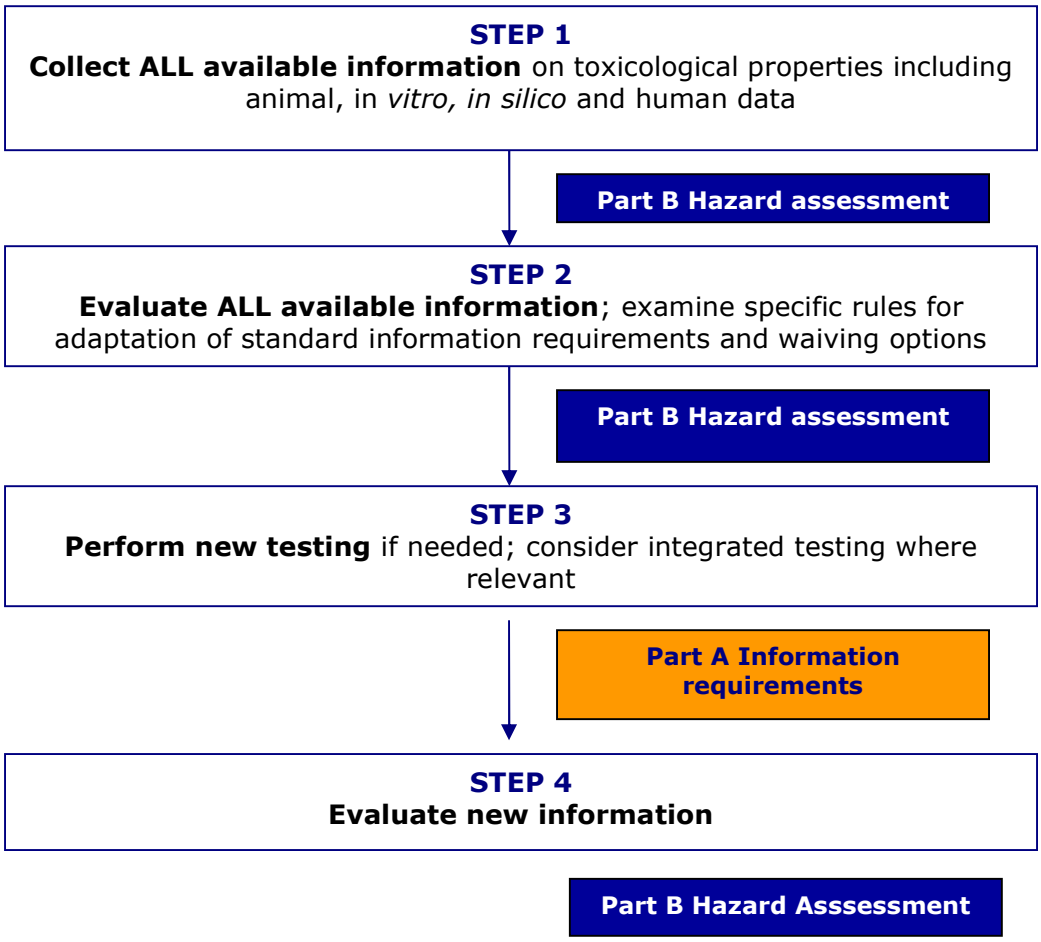


Figure 2 Schematic representation of stepwise approach for fulfilling information requirements for the purpose of the BPR
(Hyperlink to the Hazard Assessment Guidance will be added)

General considerations for animal data reporting

Where submitted, historical control data should be from the same species and strain, maintained under similar conditions in the same laboratory and should be from contemporaneous studies. Additional historical control data from other laboratories may be reported separately as supplementary information.

The information on historical control data provided should include:

(a) identification of species and strain, name of the supplier, and specific colony identification, if the supplier has more than one geographical location;

(b) name of the laboratory and the dates when the study was performed;

(c) description of the general conditions under which animals were maintained, including the type or brand of diet and, where possible, the amount consumed;

(d) approximate age, in days, and weight of the control animals at the beginning of the study and at the time of sacrifice or death;

(e) description of the control group mortality pattern observed during or at the end of the study, and other pertinent observations (such as diseases, infections);

(f) name of the laboratory and the examining scientists responsible for gathering and interpreting the pathological data from the study;
(g) for carcinogenicity studies: a statement of the nature of the tumours that may have been combined to produce any of the incidence data.

The historical control data should be presented on a study by study basis giving absolute values plus percentage and relative or transformed values where these are helpful in the evaluation. If combined or summary data are submitted, these should contain information on the range of values, the mean, median and, if applicable, standard deviation.

The doses tested, including the highest dose tested, should be selected on the basis of the results of short-term testing and where available at the time of planning the studies concerned, on the basis of metabolism and toxicokinetic data. Dose selection should consider toxicokinetic data such as saturation of absorption measured by systemic availability of active substance and/or metabolites.

Doses causing excessive toxicity should not be considered relevant to evaluations to be made. Determination of blood concentration of the active substance (for example around Tmax) should be considered in long-term repeated dose toxicity studies.

8.1. Skin irritation or skin corrosion

The assessment of this endpoint shall be carried out according to the sequential testing strategy for dermal irritation and corrosion set out in the Appendix to Test Guideline B.4. Acute Toxicity - Dermal Irritation/Corrosion (Annex B.4. to Regulation (EC)440/2008).

Steps 1 and 2 Collection and evaluation of available information
Further guidance regarding the assessment of existing information (non-human data: physicochemical properties, grouping, (Q)SARs and expert systems, *in vitro* data; human data and animal data) is available within the Guidance on the Application of the CLP Criteria (ECHA, 2012a) and Part B Human Health Effects Assessment (BPR guidance under development).

In principle information requirements for skin irritation/corrosion do not apply in cases when:

1. The available information already indicates that the criteria are met for classification as corrosive to the skin or as a skin irritant.
2. The substance is a strong acid (pH < 2) or base (pH > 11.5).
3. The substance is spontaneously flammable in air at room temperature.
4. The substance is classified as very toxic in contact with skin.
5. An acute toxicity study by the dermal route does not indicate skin irritation up to the limit dose level (2000 mg / kg body weight).

Step 3 Generation of new test data
If after the analysis in steps 1 and 2 above further testing is needed to assess the potential for skin irritation or skin corrosion, the following test methods should be used. In addition to the test methods mentioned below, new OECD validated tests for skin irritation/corrosion should be taken into account, once available, in deciding the test strategy. The OECD Test Guideline programme as well as non-animal test methods that undergo validation available by ECVAM should be regularly consulted for any updates.

The tests will provide information on the degree and nature of skin especially with regard to the reversibility of responses.

1. Testing for skin corrosion (*in vitro* assays)

If after the analysis in steps 1 and 2 above further testing is needed to assess the potential for skin corrosion, one of the following methods should be used.

Test methods for skin corrosion

- EC method B.40 *In vitro* skin corrosion: Transcutaneous Electrical Resistance Test (TER);
- OECD Test Guideline 430: *In vitro* Skin Corrosion: Transcutaneous Electrical Resistance Test;
- EC method B.40 bis *In vitro* skin corrosion: Human Skin Model Test;
- OECD Test Guideline 431: *In vitro* Skin Corrosion: Human Skin Model Test;
- OECD Test Guideline 435: *In vitro* Membrane Barrier Test Method for Skin Corrosion.

Specific limitations that may be described within the Test Guideline protocol should be taken into account before performing a test or during the interpretation of the test results acquired.

If the substance demonstrates corrosive properties following testing according to one of the available OECD and/or EC test guidelines for skin corrosion the Guidance on the Application of the CLP Criteria (ECHA, 2012a) regarding classification for skin corrosion must be considered.
If the substance does not demonstrate corrosive properties in one of the available OECD and/or EC test guidelines for skin corrosion, proceed to testing for skin irritation as described below.

2. Testing for skin irritation (*in vitro* assays)

To examine the skin irritation potential of an active substance, the following assays should be used.
Test methods for skin irritation

- EC method B.46 *In vitro* skin irritation: reconstructed human epidermis model test;
- OECD Test Guideline 439: *In vitro* Skin Irritation: Reconstructed Human Epidermis Test Method.

Specific limitations that may be described within the Test Guideline protocol should be taken into account before performing a test or during the interpretation of the test results acquired.

3. Testing for skin irritation (*in vivo* assays)

On a case-by-case basis, if specific limitations apply for the conduct of the *in vitro* test to examine skin irritation potential of the substance, as a last resort and with adequate justification *in vivo* testing may be performed with the following test guideline protocol: EC method B.4 Acute Toxicity: Dermal Irritation/Corrosion, OECD Test Guideline 404: Acute Dermal Irritation/Corrosion.

8.2. Eye irritation

The assessment of this endpoint shall be carried out according to the sequential testing strategy for eye irritation and corrosion as set down in the Appendix to Test Guideline B.5.Acute Toxicity: Eye Irritation/Corrosion (Annex B.5. to Regulation (EC) No 440/2008).

Steps 1 and 2 Collection and evaluation of available information
Further guidance regarding the assessment of existing information (non-human data: physicochemical properties, grouping, (Q)SARs and expert systems, *in vitro* data; human data and animal data) is available within the Guidance on the Application of the CLP Criteria (ECHA, 2012a) and Part B Human Health Effects Assessment (BPR guidance under development).

In principle information requirements for eye irritation do not apply in cases when:

1. The available information already indicates that the criteria are met for classification of the substance as irritating to eyes or causing serious damage to eyes, or
2. The substance is classified as corrosive to the skin, or
3. The substance is a strong acid (pH<2,0) or base (pH >11,5), or
4. The substance is spontaneously flammable in air at room temperature.

Step 3 Generation of new test data
If after the analysis in steps 1 and 2 above further testing is needed to assess the potential for eye irritation, the following test methods should be used. In addition to the test methods mentioned below, new OECD validated tests for eye irritation should be taken into account once available in deciding the test strategy. The OECD Test Guideline programme as well as non-animal test methods that undergo validation available by ECVAM should be regularly consulted for any updates.

The tests will provide information on the degree and nature of eye and associated mucous membrane irritation, especially with regard to the reversibility of responses.

i. Testing for eye irritation (*in vitro* assays)

If after the analysis in steps 1 and 2 above further testing is needed to assess the potential for eye irritation, one of the following assays should be used.

Test methods for eye irritation:

- OECD Test Guideline 437: Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants.
- EC method B.47 Bovine corneal opacity and permeability test method for identifying ocular corrosives and severe irritants (Annex of Regulation (EC) No 1152/2010).
- OECD Test Guideline 438: Isolated Chicken Eye Test Method for Identifying Ocular Corrosives and Severe Irritants.
- EC method B.48 Isolated chicken eye test method for identifying ocular corrosives and severe irritants (Annex of Regulation (EC) No 1152/2010).

Specific limitations that may be described within the Test Guideline protocol should be taken into account before performing a test or during the interpretation of the test results acquired.

The test methods mentioned above are suitable for the identification of occular corrosives and severe irritants. Where negative results are obtained, the assessment of eye irritation using a *in vitro* test method suitable also for the identification of non-irritants should follow, if a validated method has become available. If such a method is not available proceed to testing for eye irritation (*in vivo* assays).

ii. Testing for eye irritation (*in vivo* assays)

In the case of negative results in *in vitro* assays described above and in the absence of suitable *in vitro* test methods for the identification of occular non-irritants and non-corrosives, an acute toxicity eye irritation test should be performed with one of the following test guideline protocols.

Test methods for eye irritation

- EC method B.5 Acute toxicity: eye irritation/corrosion.
- OECD Test Guideline 405: Acute eye irritation/corrosion.

Respiratory Irritation

There are currently no standard tests and no OECD TG available for respiratory irritation and there is no testing requirement for respiratory irritation under the Biocides Regulation. Consequently respiratory irritation is not included in the testing strategies suggested in this Guidance. Nevertheless, account should be taken of any existing and available data that provide evidence of the respiratory irritation potential of a substance. Moreover, the data on local dermal or ocular corrosion/irritation might contain information that is relevant for the respiratory endpoint and this should be considered accordingly. Furthermore, information from cases where symptoms have been described associated with occupational exposures can be used on a case-by-case basis to characterise the respiratory irritation potency of a substance. Information from acute and repeated dose inhalation toxicity studies may also be considered sufficient to show that the substance causes respiratory irritation at a specific concentration level or range. The data need to be carefully evaluated with regard to the exposure conditions (sufficient documentation required). Possible confounding factors should be taken into account.

Additional considerations for the evaluation of all available data with regard to respiratory irritation are provided in Part B (Effects Assessment, BPR guidance under development).

8.3. Skin sensitisation

The assessment of this endpoint shall comprise the following consecutive steps:

1. *an assessment of the available human, animal and alternative data.*
2. *in vivo testing.*

Steps 1 and 2 Collection and evaluation of available information
Assessment of the available human, animal and alternative data.

Further guidance regarding the assessment of existing information (non-human data: physicochemical properties, grouping, (Q)SARs and expert systems, *in vitro* data; human data and animal data) is available within the Guidance on the Application of the CLP Criteria (ECHA, 2012a) and Part B Human Health Effects Assessment (BPR guidance under development).

In addition, *in vivo testing does not need to be conducted if:*

- *the available information indicates that the substance should be classified for skin sensitisation or corrosivity, or*
- *the substance is a strong acid (pH < 2,0) or base (pH > 11,5).*

However, the decision on the need to test a substance for skin sensitisation when it fulfils one or both of the above conditions requires expert judgment. This is because the information on skin sensitisation from the active substance will be used for the assessment of this property for products containing the substance, it needs to be taken into account whether sub-corrosive concentrations of a substance may still have sensitising properties (see Chapter III Section 8.3. also). The decision-making process on the testing for a corrosive or strong acid or strong base substance needs to take into account all the available information as specified in steps 1 and 2 above. Any limitation of the additivity concept specified in the Guidance on the Application of the CLP Criteria (ECHA, 2012a) for sensitisation with regard to addressing sub corrosive concentrations with sensitising potential should also be considered in relation to the use of the data from the active substance for assessing the sensitising potential of the biocidal product.

Step 3 Generation of new test data
If after the analysis in steps 1 and 2 above, further testing is needed to assess the potential for skin sensitisation, the following test methods should be used. In addition to the test methods mentioned below, new OECD validated tests for skin sensitisation should be taken into account once available in deciding the test strategy. The OECD Test Guideline programme as well as non-animal test methods that undergo validation available by ECVAM should be regularly consulted for any updates.

1. Testing for skin sensitisation (*in vivo* testing)

The Murine Local Lymph Node Assay (LLNA) including, where appropriate, the reduced variant of the assay, is the first-choice method for in vivo testing.

Test methods for skin sensitisation:

- EC method B.42 Skin sensitisation: Local lymph node assay.
- OECD Test Guideline 429: Skin Sensitisation – Local Lymph Node Assay.
- OECD Test Guideline 442A: Skin Sensitisation – Local Lymph Node Assay: DA.

- OECD Test Guideline 442B: Skin Sensitisation – Local Lymph Node Assay: BrdU-ELISA.

The information provided by the LLNA assay should be adequate for the derivation of threshold levels for skin sensitisation. Specific limitations that may be described within the Test Guideline protocol should be taken into account before performing a test or during the interpretation of the test results acquired.

If another skin sensitisation test is used, justification shall be provided.
If the LLNA assay is not considered suitable for a specific class of chemicals other OECD Test Guideline protocols can be used for the assessment of skin sensitisation such as:

- EC method B.6: Skin Sensitisation.
- OECD Test Guideline 406: Skin Sensitisation.

8.4. Respiratory sensitisation (ADS)

There are currently no standard tests and no OECD test guidelines available for respiratory sensitisation. Since an active substance identified as a skin sensitiser can potentially induce a hypersensitivity reaction, potential respiratory sensitisation and respiratory elicitation after dermal sensitisation should be taken into account when appropriate tests are available or when there are indications of respiratory sensitisation effects.

The assessment of the potential of a substance to induce respiratory sensitisation should include assessment of the available existing information (non-human data: physico-chemical properties, grouping, (Q)SARs and expert systems, *in vitro* data; human data and animal data), the outcome of immunotoxicity assessment (see Chapter Section 8.13.4 in this document), as well as consideration of the Guidance on the Application of the CLP Criteria (ECHA, 2012a) and Part B effects assessment (BPR guidance under development).

The following information where available should be provided:

- Information on the sensitisation/allergenicity of workers and others exposed must be provided and included, and where relevant, any incidence of hypersensitivity.
- Reports should include details of frequency, level, duration, symptoms observed, size of exposed population and other relevant data.
- Evidence that the substance can induce specific respiratory hypersensitivity will usually be based on human experience data. The clinical history data including both medical and occupational history, and reports from appropriate lung functions tests related to exposure to the substance should be submitted, if available.
- Reports of other supportive evidence must also be submitted, e.g.
    - A chemical structure related to substances known to cause respiratory hyper-sensitivity;
    - *In vivo* immunological tests;
    - *In vitro* immunological tests;
    - Studies indicating other specific but non-immunological mechanisms of action; and
    - Data from a positive bronchial challenge test.

8.5. Mutagenicity

The assessment of this endpoint shall comprise the following consecutive steps:

- *an assessment of the available in vivo genotoxicity data*

- *an in vitro test for gene mutations in bacteria, an in vitro cytogenicity test in mammalian cells and an in vitro gene mutation test in mammalian cells are required*
- *appropriate in vivo genotoxicity studies shall be considered in case of a positive result in any of the in vitro genotoxicity studies*

The testing of genotoxicity is a screening program to identify substances which might cause permanent transmissible changes in the amount or structure of a single gene or gene segments, a block of genes or chromosomes.

The aim of genotoxicity testing is to:

- predict genotoxic potential;
- identify genotoxic carcinogens at an early stage;
- elucidate the mechanism of action of some carcinogens and reproductive or developmental toxicants inducing germ-line mutations, which may lead to inherited disorders.

Appropriate dose levels, depending on the test requirements, should be used in either in vitro or *in vivo* assays. A tiered approach should be adopted, with selection of higher tier tests being dependent upon interpretation of results at each stage.

At least one *in vitro* test for gene mutations in bacteria, one test for cytogenicity in mammalian cells and one test for gene mutation in mammalian cells are required.

Steps 1 and 2 Collection and evaluation of available information
For the assessment of existing information (non-human data: physicochemical properties, grouping, (Q)SARs and expert systems, *in vitro* data; human data and animal data) further guidance is available within the Guidance on the Application of the CLP Criteria (ECHA, 2012a) and Part B Human Health Effects Assessment (BPR guidance under development)).

Step 3 Generation of new test data
If after the analysis in steps 1 and 2 above, further testing is needed to assess the potential for genotoxicity *in vitro*, the following test methods should be used. In addition to the test methods mentioned below, new OECD validated tests for genotoxicity should be taken into account once available in deciding the test strategy. The OECD Test Guideline programme as well as non-animal test methods that undergo validation available by ECVAM should be regularly consulted for any updates.

(a) Testing for genotoxicity (*in vitro* assays)

The test guideline protocols to follow for the investigation of *in vitro* genotoxicity are listed below (Chapter II Sections 8.5.1-8.5.3). These should be used taking into account some considerations described here but also taking into account the existing information for this endpoint and its assessment (see steps 1 and 2).

If gene mutation and clastogenicity/aneuploidy are detected in a battery of tests consisting of Ames and *in vitro* micronucleus (IVM), no further *in vitro* testing needs to be conducted.

If there are indications of micronucleus formation in an *in vitro* micronucleus assay further testing with appropriate staining procedures should be conducted to clarify if there is an aneugenic or clastogenic response. Further investigation of the aneugenic response may be considered to

determine whether there is sufficient evidence for a threshold mechanism and threshold concentration for the aneugenic response (particularly for non-disjunction).

Active substances which display highly bacteriostatic properties as demonstrated in a range finding test should be tested in at least one *in vitro* mammalian cell test for gene mutation, either a Mouse Lymphoma Assay (MLA) or an Hprt gene mutation assay. Non-performance of the Ames test should be justified.

For active substances bearing structural alerts that have given negative results in the standard test battery, additional testing may be required if the standard tests have not been optimised for these alerts. The choice of an additional study or study plan modifications depends on the chemical nature, the known reactivity and the metabolism data on the structurally alerting active substance.

8.5.1. *In vitro* gene mutation study in bacteria

Test methods for *in vitro* gene mutation in bacteria:

- EC method B.13/14 Mutagenicity - reverse mutation test using bacteria.
- OECD Test Guideline 471: Bacterial Reverse Mutation Test.

8.5.2. *In vitro* cytogenicity study in mammalian cells

Test methods for *in vitro* cytogenicity in mammalian cells:

- OECD Test Guideline 487. *In vitro* Mammalian Cell Micronucleus Test.[8]
- EC method B.10 Mutagenicity - *In vitro* mammalian chromosome aberration test.
- OECD Test Guideline 473: *In vitro* Mammalian Chromosome Aberration Test.
- *In vitro* Comet assay could be used when justified.

The *in vitro* cell micronucleus test can, with the current state of knowledge, be considered as the preferred method for examining *in vitro* cytogenicity in mammalian cells due to its increased sensitivity and ability to identify aneugens.

8.5.3. *In vitro* gene mutation study in mammalian cells

Test methods for *in vitro* gene mutation in mammalian cells

- EC method B.17 – Mutagenicity – *In vitro* mammalian cell gene mutation test - For this test the mouse lymphoma assay is recommended.
- OECD Test Guideline 476: *In vitro* Mammalian Cell Gene Mutation Test - For this test the mouse lymphoma assay is recommended.
- *In vitro* Comet assay could be used when justified.

8.6. *In vivo* genotoxicity study (ADS)

Steps 1 and 2 Collection and evaluation of available information
For the assessment of existing information (non-human data: physicochemical properties, grouping, (Q)SARs and expert systems, *in vitro* data; human data and animal data) further guidance is available within the Guidance on the Application of the CLP Criteria (ECHA, 2012a) and Part B Human Health Effects Assessment (BPR guidance under development)).

[8] http://lysander.sourceoecd.org/vl=17007737/cl=14/nw=1/rpsv/cgi-bin/fulltextew.pl?prpsv=/ij/oecdjournals/1607310x/v1n4/s62/p1.idx

The in vivo genotoxicity study/ies do(es) not generally need to be conducted if:

- *The results are negative for the three in vitro tests and if no metabolites of concern are formed in mammals; or*
- *Valid in vivo micronucleus data is generated within a repeat dose study and the in vivo micronucleus test is the appropriate test to be conducted to address this information requirement;*
- *The substance is known to be carcinogenic category 1A or 1B or mutagenic category 1A, 1B or 2.*

Step 3 Generation of new test data

If after the analysis in steps 1 and 2 above, further testing is needed to assess the potential for genotoxicity *in vivo*, the following test methods should be used. In addition to the test methods mentioned below, new OECD validated tests for genotoxicity should be taken into account once available in deciding the test strategy. The OECD Test Guideline programme as well as non-animal test methods that undergo validation available by ECVAM should be regularly consulted for any updates.

(b) Testing for genotoxicity (*in vivo* assays)

***In vivo* studies in somatic cells**

- *If there is a positive result in any of the in vitro genotoxicity studies (in vitro gene mutation study in bacteria, in vitro cytogenicity study in mammalian cells or in vitro gene mutation study in mammalian cells) and there are no results available from an in vivo study already, an appropriate in vivo somatic cell genotoxicity study shall be proposed / conducted by the applicant.*
- *If either of the in vitro gene mutation tests is positive, an in vivo test to investigate unscheduled DNA synthesis shall be conducted.*

However specific considerations on the limitations of the UDS assay should be taken into account before deciding on the most appropriate *in vivo* test to conduct especially with regard to the impact the results will have on potential classification and labelling. Future recommendations from the OECD Test Guideline programme with regard to *in vivo* genotoxicity testing should be followed.

- *A second in vivo somatic cell test may be necessary, depending on the results, quality and relevance of all the available data.*

Before any decisions are made about the need for *in vivo* testing, a review of the *in vitro* test results and all available information on the toxicokinetic and toxicodynamic profile of the test substance is needed. A particular *in vivo* test should be conducted only when it can be reasonably expected from all the properties of the test substance and the proposed test protocol that the specific target tissue will be adequately exposed to the test substance and/or its metabolites. If necessary, a targeted investigation of toxicokinetics should be conducted before progressing to *in vivo* testing (e.g. a preliminary toxicity test to confirm that absorption occurs and that an appropriate dose route is used).

Consideration should be given to conducting an *in vivo* test as part of one of the short-term toxicity studies described under Chapter II Section 8.9.

In the interest of ensuring that the number of animals used in genotoxicity tests is kept to a minimum, both males and females should not automatically be used. In accordance with standard guidelines, testing in one sex only is possible when the substance has been investigated for general toxicity and no sex-specific differences in toxicity have been observed.

If the *in vitro* mammalian chromosome aberration test or the *in vitro* micronucleus test is positive for clastogenicity, an *in vivo* test for clastogenicity using somatic cells such as metaphase analysis in rodent bone marrow or micronucleus test in rodents should be conducted.

In case of positive result in the *in vivo* micronucleus assay, appropriate staining procedure such as fluorescence in-situ hybridisation (FISH) should be used to identify an aneugenic and/or clastogenic response.

If either of the *in vitro* gene mutation tests is positive, an *in vivo* test to investigate the induction of gene mutation should be conducted, such as the Transgenic Rodent Somatic and Germ Cell Gene Mutation Assay.

When conducting *in vivo* genotoxicity studies, only relevant exposure routes and methods (*such as* admixture to diet, drinking water, skin application, inhalation, gavage) should be used. There should be convincing evidence that the relevant tissue will be reached by the chosen exposure route and application method. Other exposure techniques (*such as* intraperitoneal or subcutaneous injection) that are likely to result in abnormal kinetics, distribution and metabolism should be justified.

The available test guideline protocols for assessing the *in vivo* genotoxic potential of a substance are listed below and reflect current state of knowledge. The choice of the most appropriate test to conduct should reflect the considerations described in this section and future recommendations or changes within the OECD Test Guideline programme for this endpoint.

Test methods for *in vivo* genotoxicity:

- EC method B.12 - Mutagenicity - *In vivo* mammalian erythrocyte micronucleus test EC method
- B.11 - Mutagenicity – *In vivo* mammalian bone-marrow chromosome aberration test
- OECD Test Guideline 474: Mammalian Erythrocyte Micronucleus Test
- OECD Test Guideline 475: Mammalian Bone Marrow Chromosome Aberration Test
- EC method B.39 Unscheduled DNA synthesis (UDS) - Test with mammalian liver cells *in vivo*
- OECD Test Guideline 486: Unscheduled DNA synthesis (UDS) - Test with mammalian liver cells *in vivo*.
- OECD Test Guideline 488: Transgenic Rodent Somatic and Germ Cell Gene Mutation Assays
- *In vivo* Comet assay could be used when justified.

Specific considerations for *in vivo* genotoxicity testing

For substances that are short-lived, reactive, *in vitro* mutagens, or for which no indications of systemic availability have been presented, an alternative strategy involving studies to focus on tissues at initial sites of contact with the body should be considered (e.g. local genotoxicity, photomutagenicity). Expert judgment should be used on a case-by-case basis to decide which tests are the most appropriate. The main options are the *in vivo* Comet assay, gene mutation tests with transgenic rodents, and DNA adduct studies. For any given substance, expert judgment, based on all the available toxicological information, will indicate which of these tests are the most appropriate. The route of exposure should be selected that best allows assessment of the hazard posed to humans. For insoluble substances, the possibility of release of active molecules in the

gastrointestinal tract may indicate that a test involving the oral route of administration is particularly appropriate.

***In vivo* studies in germ cells**

- *If there is a positive result from an in vivo somatic cell study available, the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence to demonstrate that the substance reached the tested organ. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered.*

The potential for substances that give positive results in *in vivo* tests for genotoxic effects in somatic cells to affect germ cells should always be considered. The same is true for substances otherwise classified as category 2 mutagens. The first step is to make an appraisal of all the available toxicokinetic and toxicodynamic properties of the test substance. Expert judgment is needed at this stage to consider whether there is sufficient information to conclude that the substance poses a mutagenic hazard to germ cells. If this is the case, it can be concluded that the substance may cause heritable genetic damage and no further testing is justified. Consequently, the substance is classified as a category 1B mutagen. If the appraisal of mutagenic potential in germ cells is inconclusive, additional investigation will be necessary. In the event that additional information about the toxicokinetics of the substance would resolve the problem, toxicokinetic investigation (i.e. not a full toxicokinetic study) tailored to address this is required. The type of mutation produced in earlier studies namely gene, numerical chromosome or structural chromosome changes, should be considered when selecting the appropriate assay.

A study for the presence of DNA adducts in gonad cells may also be considered. If germ cell testing is to be undertaken, and this should be in exceptional circumstances, expert judgment should be used to select the most appropriate test strategy. Internationally recognised guidelines are available for investigating clastogenicity in rodent spermatogonial cells and for the dominant lethal test. Dominant lethal mutations are believed to be primarily due to structural or numerical chromosome aberrations.

Alternatively, other methods can be used if deemed appropriate by expert judgment. These may include the Comet assay, gene mutation tests with transgenic animals, or DNA adduct analysis.

In order to minimise animal use, the possibility to combine germ cell genotoxicity tests and reproductive toxicity tests should be considered.

The available test guideline protocols for assessing the *in vivo germ cell mutagenicity* of a substance are listed below and reflect current state of knowledge. The choice of the most appropriate test to conduct should reflect the considerations described in this section and future recommendations or changes within the OECD Test Guideline programme for this endpoint.

Test methods for *in vivo* germ cell genotoxicity:

- EC method B.23 Mammalian spermatogonial chromosome aberration test.
- OECD Test Guideline 483: Mammalian Spermatogonial Chromosome Aberration Test**.**
- OECD Test Guideline 488: Transgenic Rodent Somatic and Germ Cell Gene Mutation Assays.

8.7. Acute toxicity

Assessment of the acute toxic potential of a chemical is necessary to determine the adverse health effects that might occur following accidental or deliberate short-term exposure.

Administration via different routes makes an overall assessment of relative acute hazard of exposure in different exposure routes possible.

- *In addition to the oral route of administration (8.7.1), for substances other than gases, the information mentioned under 8.7.2 to 8.7.3 shall be provided for at least one other route of administration.*
- *The choice for the second route will depend on the nature of the substance and the likely route of human exposure.*
- *Gases and volatile liquids should be administered by the inhalation route*
- *If the only route of exposure is the oral route, then information for only that route need be provided. If either the dermal or inhalation route is the only route of exposure to humans then an oral test may be considered. Before a new dermal acute toxicity study is carried out, an in vitro dermal penetration study (OECD 428) should be conducted to assess the likely magnitude and rate of dermal bioavailability*
- *There may be exceptional circumstances where all routes of administration are deemed necessary*

Steps 1 and 2 Collection and evaluation of available information
For the assessment of existing information (non-human data: physicochemical properties, grouping, (Q)SARs and expert systems, *in vitro* data; human data and animal data) further guidance is available within the Guidance on the Application of the CLP Criteria (ECHA, 2012a) and Part B Human Health Effects Assessment (BPR guidance under development).

The study/ies do(es) not generally need to be conducted if:
- *The substance is classified as corrosive to the skin.*

8.7.1. By oral route

- *The study need not be conducted if the substance is a gas or a highly volatile substance.*

Step 3 Generation of new test data
If after the analysis in steps 1 and 2 above, further testing is needed to assess the potential for acute toxicity by the oral route, the following test methods should be used. In addition to the test methods mentioned below, new OECD validated tests for acute toxicity should be taken into account once available in deciding the test strategy. The OECD Test Guideline programme as well as non-animal test methods that undergo validation available by ECVAM should be regularly consulted for any updates.

Test methods for Acute toxicity via oral route:
- EC method B.1 tris Acute oral toxicity - Acute toxic class method.
- OECD Test Guideline 423: Acute oral toxicity: acute toxic class method.
- EC method B.1 bis Acute oral toxicity - fixed dose procedure.
- OECD Test Guideline 420: Acute oral toxicity: fixed dose procedure.
- OECD Test Guideline 425: Acute oral toxicity: up-and-down procedure.
- OECD Test Guideline 401: Acute oral toxicity (only acceptable, if performed before December 2002).

The choice of the protocol to follow for this endpoint should take into account animal welfare issues and the OECD TG 420 should be considered as the first choice for testing regarding acute toxicity.

8.7.2. By inhalation

Step 3 Generation of new test data
If after the analysis in steps 1 and 2 above, and the considerations listed below, further testing is needed to assess the potential for acute toxicity by inhalation, the following test methods should be used. In addition to the test methods listed in this section, new OECD validated tests for acute inhalation toxicity should be taken into account once available in deciding the test strategy. The OECD Test Guideline programme as well as non-animal test methods that undergo validation available by ECVAM should be regularly consulted for any updates.

Testing by the inhalation route is appropriate if exposure of humans via inhalation is likely taking into account:

- *the vapour pressure of the substance (a volatile substance has vapour pressure > 1 x 10^{-2} Pa at 20 °C) and/or*
- *the active substance is a powder containing a significant proportion (e.g. 1 % on a weight basis) of particles with particle size MMAD < 50 micrometers or*
- *the active substance is included in products that are powders or are applied in a manner that generates exposure to aerosols, particles or droplets of an inhalable size (MMAD <50 micrometers)*
- *the Acute Toxic Class Method is the preferred method for the determination of this endpoint*

If there is absence of information on particle/droplet size and where there is potential for exposure via inhalation from the use of biocidal products containing the active substance, an acute inhalation study should be performed.

Test methods for Acute toxicity via inhalation route:

- EC method B.2 Acute toxicity (inhalation).
- OECD Test Guideline 403: Acute Inhalation Toxicity.
- OECD Test Guideline 436: Acute Inhalation Toxicity – Acute Toxic Class Method.

The full study using three dose levels may not be necessary if a substance at an exposure concentration equal to the limit concentrations of the test guideline (limit test) or at the maximum attainable concentration produces no compound-related mortalities.

The head/nose only exposure should be used, unless whole body exposure can be justified.

8.7.3. By dermal route

Step 3 Generation of new test data
Testing by the dermal route is necessary only if:

- *inhalation of the substance is unlikely, or*
- *skin contact in production and/or use is likely, and either*
- *the physicochemical and toxicological properties suggest potential for a significant rate of absorption through the skin, or*
- *the results of an in vitro dermal penetration study (OECD 428) demonstrate high dermal absorption and bioavailability.*

Dermal toxicity must be reported for an active substance except for gases.

If after the analysis in steps 1 and 2 above, further testing is needed to assess the potential for acute toxicity by the dermal route, the following test methods should be used. In addition to the

test methods mentioned below, new OECD validated tests for acute dermal toxicity should be taken into account once available in deciding the test strategy. The OECD Test Guideline programme as well as non-animal test methods that undergo validation available by ECVAM should be regularly consulted for any updates.

Test methods for Acute toxicity via dermal route:

- EC method B.3 Acute toxicity (dermal).
- OECD Test Guideline 402: Acute Dermal Toxicity.

For substances with low acute dermal toxicity a limit test with 2000 mg/kg body weight may be sufficient.

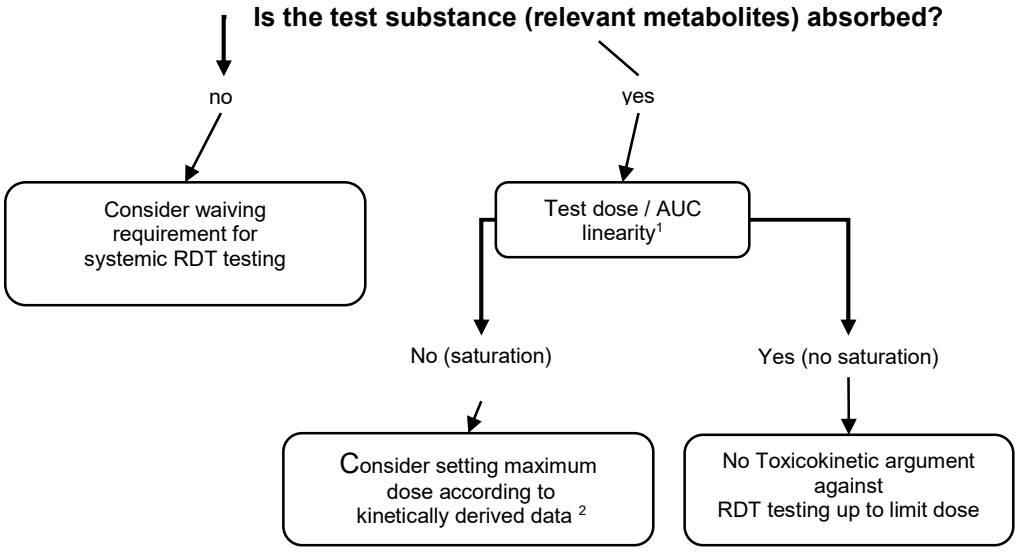
8.8. Toxicokinetics and metabolism studies in mammals

The toxicokinetics and metabolism studies should provide basic data about the rate and extent of absorption, the tissue distribution and the relevant metabolic pathway including the degree of metabolism, the routes and rate of excretion and the relevant metabolites.

The generation of toxicokinetics data should be considered in light of the generation of other toxicity data (i.e. repeated dose toxicity, mutagenicity, and reproductive toxicity) to assist in the estimation of internal exposure to the active substance and/or its metabolites and the correlation of the effects observed with internal dose estimates. The latter is of particular importance for establishing the mode of action of the active substance and whether administered doses caused saturation kinetics resulting in a non-linear dose-response. Such information is valuable for the derivation of assessment factors, route-to-route extrapolation and hazard characterisation.

Steps 1 and 2 Collection and evaluation of available information
For the assessment of existing information (non-human data: physicochemical properties, grouping, (Q)SARs and expert systems, *in vitro* data; human data and animal data) further guidance is available within Part B Human Health Effects Assessment (BPR guidance under development)).

Step 3: Generation of new test data
Following the evaluation of all available data, a decision should be made on which type of kinetic data and which test design is most appropriate. It is preferred to generate kinetic data within the toxicity studies such as repeated dose toxicity where possible. The sections below describe the issues to consider when designing new tests for toxicokinetics and the available techniques for the tests suitable for ADME (absorption, distribution, metabolism, elimination) estimation. The importance of the toxicokinetic data within the design of repeated dose toxicity as well as the refinement of the assessment of the results from toxicity studies is presented in Figure 3 and Figure 4 (adopted from ECHA Guidance R7C, (ECHA, 2012c)).



[1] In the dose-range under consideration for RDT testing

[2] Meaning that the highest dose-level should not exceed the range of non-linear kinetics.

Figure 3 Use of toxicokinetic data in the design of repeated dose toxicity studies

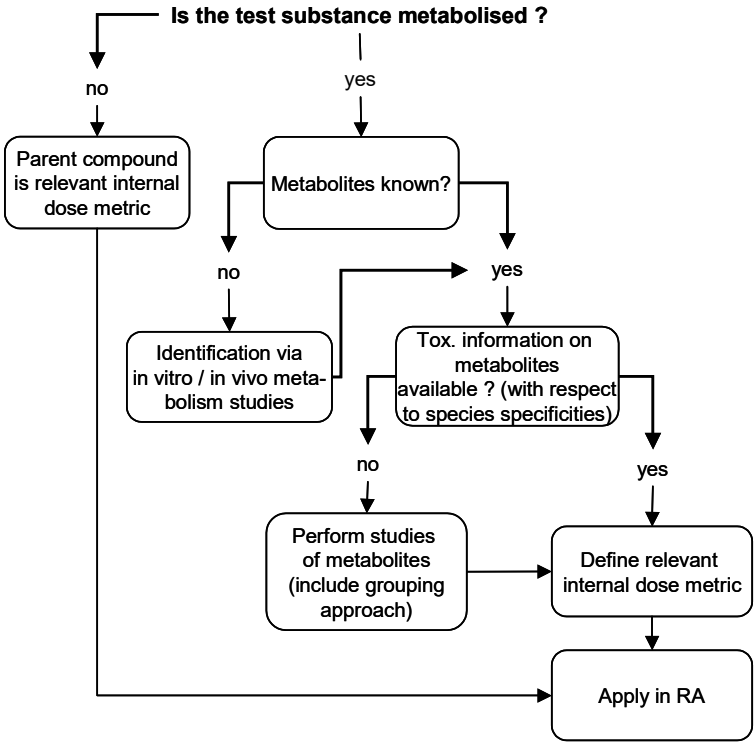


Figure 4 Use of increasing knowledge on substance metabolism

The OECD Test Guideline 417 provides the protocol for the conduct of toxicokinetic studies either as standalone test or in combination with repeated dose toxicity studies.

In vivo studies provide an integrated perspective on the relative importance of different processes in the intact biological system for comparison with the results of the toxicity studies. To ensure a valid set of toxicokinetic data, a toxicokinetic *in vivo* study has to consist of several experiments that include blood/plasma-kinetics, mass balances and excretion experiments as well as tissue distribution experiments. Depending on the problem to be solved, selected experiments (e.g. plasma-kinetics) may be sufficient to provide needed data for further assessments (e.g. bioavailability).

The high dose level administered in an ADME study should be linked to the dose levels that cause adverse effects in toxicity studies. Ideally there should also be a dose without toxic effect, which should be in the range of expected human exposure including consideration of limit of quantification. A comparison between toxic dose levels and those that are likely to represent human exposure values may provide valuable information for the interpretation of adverse effects and is essential for extrapolation and risk assessment.

In an *in vivo* study the systemic bioavailability is usually estimated by the comparison of either dose-corrected amounts excreted, or of dose-corrected areas under the curve (AUC) of plasma (blood, serum) kinetic profiles, after extra- and intravascular administration. The systemic bioavailability is the dose-corrected amount excreted or AUC determined after an extravascular substance administration divided by the dose-corrected amount excreted or AUC determined after an intravascular substance application, which corresponds by definition to a bioavailability of 100%. This is only valid if the kinetics of the compound is linear, i.e. dose-proportional, and relies upon the assumption that the clearance is constant between experiments. If the kinetics is not linear, the experimental strategy has to be revised on a case-by-case basis, depending of the type of non-linearity involved (e.g. saturable protein binding, saturable metabolism, etc).

Generally *in vitro* studies provide data on specific aspects of pharmacokinetics such as metabolism. A major advantage of *in vitro* studies is that it is possible to carry out parallel tests on samples from the species used in toxicity tests and samples from humans, thus facilitating interspecies comparisons (e.g., metabolite profile, metabolic rate constants). In recent years methods to integrate a number of *in vitro* results into a prediction of ADME *in vivo* by the use of appropriate physiologically based kinetic (PBK) models have been developed. Such methods allow both the prediction of *in vivo* kinetics at early stages of development, and the progressive integration of all available data into a predictive model of ADME. The resulting information on ADME can be used both to inform development decisions and as part of the risk assessment process. The uncertainty associated with the prediction depends largely on the amount of available data.

Information on blood and tissues concentration of the active substance and relevant metabolites, for example around the time to reach the maximum plasma concentration (T_{max}) or other relevant toxicokinetic parameter, should be generated in short and long-term studies on relevant species to enhance the value of the toxicological data generated in terms of understanding the toxicity studies. If such information is not considered essential for the assessment, full justification should be provided.

The main objective of the toxicokinetic data is to describe the systemic exposure achieved in animals and its relationship to the dose levels and the time course of the toxicity studies.
Other objectives are:

(a) to relate the achieved exposure in toxicity studies to toxicological findings and contribute to the assessment of the relevance of these findings to human health, with a particular regard to vulnerable groups;

(b) to support the design of a toxicity study (choice of species, treatment regimen, selection of dose levels) with respect to kinetics and metabolism;
(c) to provide information which, in relation to the findings of toxicity studies, contributes to the design of supplementary toxicity studies.

Absorption, distribution, metabolism and excretion after exposure by oral route
Limited data restricted to one *in vivo* test species (normally rat) may be all that is required as regards absorption, distribution, metabolism and excretion after exposure by oral route. These data can provide information useful in the design and interpretation of subsequent toxicity tests. However, it should be remembered that information on interspecies differences is crucial in extrapolation of animal data to humans and information on metabolism following administration via other routes may be useful in human risk assessments.

It is not possible to specify detailed data information requirements in all areas, since the exact requirements will depend upon the results obtained for each particular test substance.

Absorption
Absorption is normally investigated by the determination of the test substance and/or its metabolites in excreta, exhaled air and carcass (i.e. radioactivity balance). The biological response between test and reference groups (e.g. oral versus i.v.) is compared and the plasma level of the test substance and/or its metabolites is determined.

Distribution
For determination of the distribution of a substance in the body there are two approaches available at present for analysis of distribution patterns. Quantitative information can be obtained firstly, using whole-body autoradiographic techniques and secondly, by sacrificing animals at different times after exposure and determination of the concentration and amount of the test substance and/or metabolites in tissues and organs (EC method B.36 'Toxicokinetics', OECD TG 417, 'Toxicokinetics').

Accumulative potential
Information derived for the purpose of environmental risk assessment can further inform human health risk assessment and the potential for a substance to accumulate. Bioconcentration refers to the accumulation of a substance dissolved in water by an aquatic organism. The static bioconcentration factor (BCF) is the ratio of the concentration of a substance in an organism to the concentration in water once a steady state has been achieved. Traditionally, bioconcentration potential has been assessed using laboratory experiments that expose fish to the substance dissolved in water (EC method C.13 'Bioconcentration: Flow-Through Fish Test', OECD TG 305 'Bioaccumulation in Fish: Aqueous and Dietary Exposure'). The resulting fish BCF is widely used as a surrogate measure for bioaccumulation potential.

If single dose toxicity and tissue distribution data are not adequate to determine the potential for accumulation, repeated dose administration may be needed to address the potential for accumulation and/or persistence or changes in toxicokinetics.

Accumulating substances can also be measured in milk and therefore additionally allow an estimation of transfer to the breast-fed pup.

Metabolism
In vivo toxicokinetics studies generally only determine the rates of total metabolic clearance (by measurement of radiolabelled products in blood/plasma, bile, and excrements) rather than the

contributions of individual tissues. It has to be taken into account that the total metabolic clearance is the sum of the hepatic and potential extrahepatic metabolism.
In vitro tests can be performed using isolated enzymes, microsomes and microsomal fractions, immortalised cell lines, primary cells and organ slices. Most frequently these materials originate from the liver as this is the most relevant organ for metabolism, however, in some cases preparation from other organs are used for investigation of potential organ-specific metabolic pathways.

When using metabolically incompetent cells an exogenous metabolic activation system is usually added into the cultures. For this purpose the post-mitochondrial 9000x g supernatant (S9 fraction) of whole liver tissue homogenate containing a high concentration of metabolising enzymes is most commonly employed - the donor species needs to be considered in the context of the study. In all cases metabolism may either be directly assessed by specific identification of the metabolites or by subtractive calculation of the amount of parent substance lost in the process.

Excretion
The major routes of excretion are in the urine and/or the faeces (via bile and directly from the GI mucosa; see (Rozman, 1986). For this purpose urine, faeces and expired air and, in certain circumstances, bile are collected and the amount of test substance and/or metabolites in these excreta is measured (EC method B.36 'Toxicokinetics', OECD TG 417 'Toxicokinetics').

The excretion of chemicals (metabolites) in other biological fluids such as *saliva*, *milk*, *tears*, and s*weat* is usually negligible compared with renal or biliary excretion. However, in special cases these fluids may be important to study either for monitoring purposes, or in the case of milk allowing an assessment of the exposure of infants.

For volatile substances and metabolites exhaled air may be an important route of elimination. Therefore, exhaled air needs to be examined in respective cases.

The use of *in silico* methods and kinetic modelling (physiologically based pharmacokinetic (PBPK) modelling) should also be considered upfront in the assessment and toxicokinetic data generation. Similarly available data from human biological monitoring and biological marker measurement studies should be part of the assessment. Further guidance on the use of these methods is provided in Part B Effect Assessment (BPR guidance under development).

Aspects to consider in the design of tests for toxicokinetic data generation

The design of the studies is case-by-case dependent and should consider generation of information about the kinetics of the active substance and its metabolites in relevant species after being exposed to the following conditions:

(a) a single oral dose (low and high dose levels);
(b) an intravenous dose preferably or, if available, a single oral dose with assessment of biliary excretion (low dose level); and
(c) a repeated dose.

A key parameter is systemic bioavailability (F), obtained by comparison of the area under the curve (AUC) after oral and intravenous dosing.

When intravenous dosing is not feasible, a justification should be provided. The design of the kinetic studies required should include:

(a) an evaluation of the rate and extent of oral absorption including maximum plasma concentration (Cmax), AUC, Tmax and other appropriate parameters, such as bioavailability;
(b) the potential for bioaccumulation;
(c) plasma half lives;
(d) the distribution in major organs and tissues;
(e) information on the distribution in blood cells;
(f) the chemical structure and the quantification of metabolites in biological fluids and tissues;
(g) the different metabolic pathways;
(h) the route and time course of excretion of active substance and metabolites;
(i) investigations whether and to what extent enterohepatic circulation takes place.

Comparative *in vitro* metabolism studies should be performed on animal species to be used in pivotal studies and on human material (microsomes or intact cell systems) in order to determine the relevance of the toxicological animal data and to guide in the interpretation of findings and in further definition of the testing strategy.

An explanation must be given or further tests should be carried out where a metabolite is detected *in vitro* in human material and not in the tested animal species.

Absorption, distribution, metabolism and excretion after exposure by other routes
Data on absorption, distribution, metabolism and excretion (ADME) following exposure by the dermal route should be provided where toxicity following dermal exposure is of concern compared to that following oral exposure. Before investigating ADME *in vivo* following dermal exposure, default values for estimating dermal uptake and excretion as described in Part B (BPR guidance under development) as well as the need to conduct an *in vitro* dermal penetration study should be considered to assess the likely magnitude and rate of dermal bioavailability.

Absorption, distribution, metabolism and excretion after exposure by the dermal route should be considered on the basis of the above information, unless the active substance causes skin irritation that would compromise the outcome of the study.

For volatile active substances (vapour pressure $>10^{-2}$ Pa at 20 °C) absorption, distribution, metabolism and excretion after exposure by inhalation may be useful in human risk assessments.

Dermal absorption
An appropriate dermal absorption assessment is needed. It is not always mandatory to submit experimental data. If such data are not available, as a first step default values (depending on physicochemical properties of the active substance) can be used (additional guidance provided in Part B of Hazard Identification within the Toxicokinetics chapter (BPR guidance under development)). The OECD Guidance Document on Percutaneous absorption/penetration (OECD, 2004a) and the EFSA Guidance Document on Dermal Absorption (EFSA, 2012) should be followed where applicable for the estimation of dermal absorption both for the active substance and the biocidal product (Chapter III Section 8.6).

The following Test Guidelines are available for the conduct of skin absorption studies:
- EC method B.45 Skin Absorption: *In Vitro* Method
- OECD Test Guideline 428: Skin Absorption: *In Vitro* Method
- EC method B.44 Skin Absorption: *In Vivo* Method
- OECD Test Guideline 427: Skin Absorption: *In Vivo* Method

If testing to assess the likely magnitude and rate of dermal bioavailability is necessary the OECD Test Guideline 428 for *in vitro* skin absorption should be considered first.

In vitro systems allow us to apply to a fixed surface area of the skin an accurate dose of a test chemical in the form, volume and concentration that are likely to be present during human exposure. One of the key parameters in the regulatory guidelines in this field is that sink conditions must always be maintained, which may bias the assay by build-up of the chemical in the reservoir below the skin[9]. A major issue of concern in the *in vitro* procedure turned out to be the presence of test substance in the various skin layers, i.e., absorbed into the skin but not passed into the receptor fluid. It was noted that it is especially difficult to examine very lipophilic substances *in vitro*, because of their low solubility in most receptor fluids. By including the amount retained in the skin *in vitro*, a more acceptable estimation of skin absorption can be obtained. Water-soluble substances can be tested more accurately *in vitro* because they more readily diffuse into the receptor fluid (OECD, 2004a). At present, provided that skin levels are included as absorbed, results from *in vitro* methods seem to adequately reflect those from *in vivo* experiments supporting their use as a replacement test to measure percutaneous absorption.

Advantages of the *in vivo* method (EC method B.44 'Skin Absorption: *In Vivo* Method', OECD TG 427 'Skin Absorption: In Vivo Method') are that it uses a physiologically and metabolically intact system, it uses a species common to many toxicity studies and can be modified for use with other species. The disadvantages are the use of animals, the need for radiolabelled material to facilitate reliable results, difficulties in determining the early absorption phase and the differences in permeability of the preferred species (rat) and human skin. Animal skin is generally more permeable and therefore may overestimate human percutaneous absorption (US EPA, 1992). The experimental conditions should also be taken into account in interpreting the results. For instance, dermal absorption studies in fur-bearing animals may not accurately reflect dermal absorption in human beings.

If appropriate dermal penetration data are available for rats *in vivo* and for rat and human skin *in vitro*, the *in vivo* dermal absorption in rats may be adjusted in light of the relative absorption through rat and human skin *in vitro*. The latter adjustment may be done because the permeability of human skin is often lower than that of animal skin (Howes, et al., 1996). A generally applicable correction factor for extrapolation to man can, however, not be derived, because the extent of overestimation appears to be dose-, substance- and animal- specific (ECETOC, 1993); (Bronaugh & Maibach, 1987). *In silico* models might also improve the overall knowledge of crucial properties significantly. Mathematical skin permeation models are usually based on uptake from aqueous solution which may not be relevant to the exposure scenario being assessed. In addition, the use of such models for quantitative risk assessment purposes is often limited because these models have generally been validated by *in vitro* data ignoring the fate of the skin residue levels. However, these models may prove useful as a screening tool or for qualitative comparison of skin permeation potential. On a case-by-case basis, and if scientifically justified, the use of (quantitative) structure activity relationships may prove useful, especially within a group of closely related substances.

Considerations for test substances and analytical methodology for toxicokinetic studies
Toxicokinetic and metabolism studies can be carried out using non-labelled compounds, stable isotope-labelled compounds, radioactively labelled compounds or using dual (stable and radio-) labelling. The labels should be placed in metabolically stable positions, the placing of labels such

[9] A build-up of chemical in the reservoir below the skin is not such a problem if a flow through cell is used for *in vitro* testing.

as ^{14}C in positions from which they can enter the carbon pool of the test animal should be avoided. If a metabolic degradation of the test substance may occur, different labelling positions have to be taken into account to be able to determine all relevant degradation pathways. The radiolabelled compound must be of high radiochemical purity and of adequate specific activity to ensure sufficient sensitivity in radio-assay methods.

Separation techniques are used in metabolism studies to purify and separate several radioactive fractions in biota such as urine, plasma, bile and others. These techniques range from relatively simple approaches such as liquid-liquid extraction and column chromatography to more sophisticated techniques such as HPLC (high pressure liquid chromatography). These methods also allow for the establishment of a metabolite profile. Quantitative analytical methods are required to follow concentrations of parent compound and metabolites in the body as a function of time. The most common techniques used are LC/MS (liquid chromatography/ mass spectroscopy) and high performance LC with UV-detection, or if ^{14}C-labelled material is used, radioactivity-detection-HPLC. It is worth mentioning that kinetic parameters generally cannot be calculated from measurement of total radioactivity to receive an overall kinetic estimate. Nevertheless, to generate exact values one has to address parent compound and metabolites separately. An analytical step is required to define the radioactivity as chemical species. This is usually faster than cold analytical methods. Dual labelling (e.g. ^{13}C and $^{14}C/^{12}C$) is the method of choice for structural elucidation of metabolites (by MS and NMR [nuclear magnetic resonance] spectroscopy). A cold analytical technique, which incorporates stable isotope labelling (for GC/MS [gas chromatography/ mass spectroscopy] or LC/MS), is a useful combination. Unless this latter method has already been developed for the test compound in various matrices (urine, faeces, blood, fat, liver, kidney, etc.), the use of radiolabelled compound may be less costly than other methods.

In any toxicokinetic study, the identity and purity of the chemical used in the test must be assured. Analytical methods capable of detecting undesirable impurities will be required, as well as methods to assure that the substance of interest is of uniform potency from batch to batch. Additional methods will be required to monitor the stability and uniformity of the form in which the test substance is administered to the organisms used in the toxicokinetic studies. Finally, methods suitable to identify and quantify the test substance in toxicokinetic studies must be employed.

In the context of analytical methods, *accuracy* refers to how closely the average value reported for the assay of a sample agrees with the actual amount of substance being assayed in the sample, whereas *precision* refers to the amount of scatter in the measured values around the average result. If the average assay result does not agree with the actual amount in the sample, the assay is said to be *biased*, i.e., lacks specificity; bias can also be due to low recovery. Assay *specificity* is perhaps the most serious problem encountered. Although *blanks* provide some assurance that no instrument response will be obtained in the absence of the test chemical, a better approach is to select an instrument or bioassay that responds to some biological, chemical, or physical property of the test chemical that is not shared with many other substances. Besides, it is also necessary that the assay method is usable over a sufficiently wide range of concentrations for the toxic chemical and its metabolites. The lower limit of reliability for an analytical method has been perceived in different ways; frequently, the term sensitivity has been used to indicate the ability of an analytical method to measure small amounts of a substance accurately and with requisite precision. It is unlikely that a single analytical method will be of use for all of these purposes. Indeed, it is highly desirable to use more than one method, at times. If two or more methods yield essentially the same results, confidence in each method is increased.

8.8.1. Further toxicokinetic and metabolism studies in mammals (ADS)

Additional studies might be required based on the outcome of the toxicokinetic and metabolism study conducted in rat. These further studies shall be required if:

- *there is evidence that metabolism in the rat is not relevant for human exposure*
- *route-to-route extrapolation from oral to dermal/inhalation exposure is not feasible.*
- *Where it is considered appropriate to obtain information on dermal absorption, the assessment of this endpoint shall proceed using a tiered approach for assessment of dermal absorption.*

With the core data set, basic information about the rate and extent of absorption, the tissue distribution and the relevant metabolic pathway including the degree of metabolism, the routes and rate of excretion and the relevant metabolites should be provided by the toxicokinetic and metabolism studies (Annex II Section 8.8). Additional information might be needed based on the outcome of the toxicokinetic and metabolism study conducted in rats (ADS according to Annex II Section 8.8.1) or based on the evaluation of the toxicological and physicochemical profile of the substance.

In some circumstances, e.g. when there are indications for a potential of the active substance to accumulate, to persist or to change the toxicokinetics e.g. by induction of metabolic enzymes, further studies with repeated administration may be necessary. Chapter II Section 8.8 provides guidance on the options available for the toxicokinetics study and its integration with the repeated dose toxicity tests.

8.9. Repeated dose toxicity

Repeated dose toxicity testing provides information on adverse effects as a result of repeated or prolonged exposure.

- *In general, only one route of administration is necessary and the oral route is the preferred route. However, in some cases it may be necessary to evaluate more than one route of exposure.*
- *For the evaluation of the safety of consumers in relation to active substances that may end up in food or feed, it is necessary to conduct toxicity studies by the oral route.*

Justification to replace the oral route by another significant route, or to require testing in addition to the oral route needs to be provided.

- *In order to reduce testing carried out on vertebrates and in particular the need for free-standing, single-endpoint studies, the design of the repeated dose toxicity studies shall take account of the possibility to explore several parameters within the framework of one study*

(e.g. kinetic data generation, micronucleus formation, neurotoxicity, immunotoxicity).

The repeated dose toxicity study (28 or 90 days) does not need to be conducted if:

- *a substance undergoes immediate disintegration and there are sufficient data on the cleavage products for systemic and local effects and no synergistic effects are expected; or*
- *relevant human exposure can be excluded in accordance with section 3 of Annex IV*

8.9.1. Short-term repeated dose toxicity study (28 days), preferred species is rat

Steps 1 and 2 Collection and evaluation of available information
For the assessment of existing information (non-human data: physicochemical properties, grouping, (Q)SARs and expert systems, *in vitro* data; human data and animal data) further guidance is available within the Guidance on the Application of the CLP criteria (ECHA, 2012a) and Part B Human Health Effects Assessment (BPR guidance under development).

In addition to the waiving option for the repeated dose toxicity studies described in Chapter II Section 8.9 *the short-term toxicity study (28 days) does not need to be conducted if:*

- *a reliable sub-chronic (90 days) study is available, provided that the most appropriate species, dosage, solvent and route of administration were used,*
- *the frequency and duration of human exposure indicates that a longer term study is appropriate and one of the following conditions is met:*
  - *other available data indicate that the substance may have a dangerous property that cannot be detected in a short-term toxicity study; or*
  - *appropriately designed toxicokinetic studies reveal accumulation of the substance or its metabolites in certain tissues or organs which would possibly remain undetected in a short term toxicity study but which are liable to result in adverse effects after prolonged exposure.*

In principle, for substances where a 90-day repeated dose toxicity study will need to be performed, an additional 28-day repeated dose toxicity study will not be required.

If a 28-day repeated dose toxicity needs to be performed the considerations described under Chapter II Section 8.9.2 regarding the generation of new test data should also be taken into account.

Step 3 Generation of new test data
If after the analysis in steps 1 and 2 above, further testing is needed to assess repeated dose toxicity, the following test methods should be used. In addition to the test methods mentioned below, new OECD validated tests for repeated dose toxicity should be taken into account once available in deciding the test strategy. The OECD Test Guideline programme as well as non-animal test methods that undergo validation available by ECVAM should be regularly consulted for any updates.

Repeated Dose toxicity (Oral)
Test methods for repeated dose toxicity via oral route:

- EC method B.7 Repeated dose (28 days) toxicity (oral).
- OECD Test Guideline 407: Repeated dose 28-day oral toxicity study in rodents.

Other routes:
Repeated Dose toxicity (dermal)
Testing by the dermal route shall be considered if:

- *skin contact in production and/or use is likely; and*
- *inhalation of the substance is unlikely; and*
- *one of the following conditions is met:*
  (i) toxicity is observed in an acute dermal toxicity test at lower doses than in the oral toxicity test; or

(ii) information or test data indicate dermal absorption is comparable or higher than oral absorption; or

(iii) dermal toxicity is recognised for structurally related substances and for example is observed at lower doses than in the oral toxicity test or dermal absorption is comparable or higher than oral absorption.

In addition, if the substance is a severe irritant or corrosive, testing by the dermal route should be avoided unless it can be performed at doses that do not cause irritation or corrosion and such doses are still toxicologically relevant and the outcome can be used in risk assessment.

The following test methods for repeated dose toxicity via dermal route should be used:

- EC method B.9 Repeated dose (28 days) toxicity (dermal)
- OECD Test Guideline 410: Repeated dose dermal toxicity: 21/28-day study.

Repeated Dose toxicity (inhalation)

Testing by the inhalation route shall be considered if:

- *exposure of humans via inhalation is likely taking into account the vapour pressure of the substance (volatile substances and gases have vapour pressure > 1 x 10^{-2} Pa at 20 °C) and/or*
- *there is the possibility of exposure to aerosols, particles or droplets of an inhalable size (MMAD <50 micrometers).*

The following test methods for repeated dose toxicity via inhalation route should be used:

- EC method B.8 Repeated dose (28 days) toxicity (inhalation)
- OECD Test Guideline 412: Subacute inhalation toxicity : 28-day study

8.9.2. Sub-chronic repeated dose toxicity study (90-day), preferred species is rat

Steps 1 and 2 Collection and evaluation of available information

For the assessment of existing information (non-human data: physicochemical properties, grouping, (Q)SARs and expert systems, *in vitro* data; human data and animal data) further guidance is available within the Guidance on the Application of the CLP Criteria (ECHA, 2012a) and Part B Human Health Effects Assessment (BPR guidance under development).

In addition to the waiving options for the repeated dose toxicity studies described in Chapter II Section 8.9, *the sub-chronic toxicity study (90 days) does not need to be conducted if:*

- *a reliable short-term toxicity study (28 days) is available showing severe toxicity effects according to the criteria for classifying the substance as H372 and H373 (Regulation (EC) No 1272/2008), for which the observed NOAEL-28 days, with the application of an appropriate uncertainty factor allows the extrapolation towards the NOAEL-90 days for the same route of exposure and;*
- *a reliable chronic toxicity study is available, provided that an appropriate species and route of administration were used; or*
- *the substance is unreactive, insoluble, not bioaccumulative and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day "limit test", particularly if such a pattern is coupled with limited human exposure.*

Step 3: Generation of new test data

If after the analysis in steps 1 and 2 above, further testing is needed to assess repeated dose toxicity, the test methods described further below should be used. In addition to the test methods mentioned below, new OECD validated tests for repeated dose toxicity should be taken into account once available in deciding the test strategy. The OECD Test Guideline programme as well as non-animal test methods that undergo validation available by ECVAM should be regularly consulted for any updates.

Considerations for the design of the repeated dose subchronic toxicity studies
The study will be performed in a single rodent species, preferably the rat. The oral route will be used unless one of the other routes is more appropriate based on either the most relevant route of human exposure or the physico-chemical properties of the substance. The other routes should be considered especially if route-to-route extrapolation is not appropriate and the predominant human exposure occurs via dermal and/or inhalation route. In the 90-day study, potential neurotoxic and immunotoxic effects (see also Chapter II, Sections 8.13.2 and 8.13.4), genotoxicity by way of micronuclei formation and effects potentially related to changes in the hormonal system (see also Chapter II Section 8.13.3) must be carefully considered during the conduct of the test and reported, taking into account potential limitations when modifying test protocols in order to investigate specific effects.

Information on mode of action from structurally similar substances should also be considered in the design of repeated dose toxicity tests.

Repeated dose toxicity studies should be designed to provide information as to the amount of the active substance that can be tolerated without adverse effects under the conditions of the study and to elucidate health hazards occurring at higher dose levels. Such studies provide useful data on the risks for those handling and using biocidal products containing the active substance, among other possible exposed groups. In particular, repeated dose toxicity studies provide an essential insight into possible repeated actions of the active substance and the risks to humans who may be exposed. In addition repeated dose toxicity studies provide information useful in the design of chronic toxicity studies.

The studies, data and information to be provided and evaluated, should be sufficient to permit the identification of effects following repeated exposure to the active substance, and in particular to further establish, or indicate:

(a) the relationship between dose and adverse effects;
(b) toxicity of the active substance including where possible the No Observed Adverse Effect Level (NOAEL);
(c) target organs, where relevant (including immune, nervous and endocrine systems);
(d) the time course and characteristics of adverse effects with full details of behavioural changes and possible pathological findings at post-mortem;
(e) specific adverse effects and pathological changes produced;
(f) where relevant the persistence and reversibility of certain adverse effects observed, following discontinuation of dosing;
(g) where possible, the mode of toxic action;
(h) the relative hazard associated with the different routes of exposure;
(i) relevant critical endpoints at appropriate time points for setting reference values, where necessary.

Toxicokinetic data (that is to say blood concentration of the active substance and/or the main metabolites) should be included in repeated dose toxicity studies, unless a justification explaining

why it is not necessary to do so is provided. In order to avoid increased animal use, the data may be derived in range finding studies.

If nervous system, immune system or endocrine system are specific targets in repeated dose toxicity studies at dose levels not producing marked toxicity, supplementary studies, including functional testing, need to be considered.

Repeated Dose Toxicity (Oral route)
The following test methods should be used.

Test methods for sub-chronic repeated dose toxicity via oral route:

- EC method B.26 Sub-chronic oral toxicity test. Repeated dose 90-day oral toxicity study in rodents.
- EC method B.27 Sub-chronic oral toxicity test. Repeated dose 90-day oral toxicity study in non-rodents.
- OECD Test Guideline 408: Repeated dose 90-day oral toxicity study in rodents.
- OECD Test Guideline 409: Repeated dose 90-day oral toxicity study in non-rodents.

Other routes

Repeated Dose Toxicity (Inhalation route)
Testing by the inhalation route shall be considered if:

- *exposure of humans via inhalation is likely taking into account the vapour pressure of the substance (volatile substances and gases have vapour pressure > 1 x 10^{-2} Pa at 20 °C) and/or*
- *there is the possibility of exposure to aerosols, particles or droplets of an inhalable size (MMAD <50 micrometers).*

The following test methods for sub-chronic repeated dose toxicity via inhalation route should be used:

- EC method B.29 Sub-chronic inhalation toxicity study 90-day repeated inhalation dose study using rodent species.
- OECD Test Guideline 413: Subchronic inhalation toxicity: 90-day study.

Repeated Dose Toxicity (Dermal route)
Testing by the dermal route shall be considered if:

- *skin contact in production and/or use is likely; and*
- *inhalation of the substance is unlikely; and*
- *one of the following conditions is met:*
  - *(i) toxicity is observed in an acute dermal toxicity test at lower doses than in the oral toxicity test; or*
  - *(ii) information or test data indicate dermal absorption is comparable or higher than oral absorption; or*
  - *(iii) dermal toxicity is recognised for structurally related substances and for example is observed at lower doses than in the oral toxicity test or dermal absorption is comparable or higher than oral absorption.*

In addition, if the substance is a severe irritant or corrosive, testing by the dermal route should be avoided unless it can be performed at doses that do not cause irritation or corrosion and such doses are still toxicologically relevant and the outcome can be used in risk assessment.

The following test methods for sub-chronic repeated dose toxicity via dermal route should be used:

- EC method B.28 Sub-chronic dermal toxicity test : 90-day repeated dermal dose study using rodent species.
- OECD Test Guideline 411: Subchronic dermal toxicity test: 90-day study.

8.9.3. Long-term repeated dose toxicity (≥ 12 months)

Any new long-term toxicity study and carcinogenicity study (Chapter II Section 8.11) should be combined. This section provides guidance covering both the long-term repeated dose toxicity and the carcinogenicity study. The test is required for one rodent, the rat being the preferred species. In exceptional cases and depending on the results obtained testing in another mammalian species (rodent or non-rodent, see also Chapter II Section 8.9.4 for tests in non-rodent species) may be considered.

Steps 1 and 2 Collection and evaluation of available information
For the assessment of existing information (non-human data: physicochemical properties, grouping, (Q)SARs and expert systems, *in vitro* data; human data and animal data) further guidance is available within the Guidance on the Application of the CLP Criteria (ECHA, 2012a) and Part B Human Health Effects Assessment (BPR guidance under development).

The long-term toxicity study (≥ 12 months) does not need to be conducted if:

- *long-term exposure can be excluded and no effects have been seen at the limit dose in the 90-day study, or*
- *a combined long-term repeated dose/carcinogenicity study (8.11.1) is undertaken.*

In addition as specified in Annex II of the BPR (8.11) when the combined long-term carcinogenicity study is performed the specific rules for adaptation for carcinogenicity apply:

A carcinogenicity study does not also need to be conducted if:

- *the substance is classified as mutagen category 1A or 1B. The default presumption would be that a genotoxic mechanism for carcinogenicity is likely. In these cases, a carcinogenicity test will normally not be required.*

Step 3: Generation of new test data
If after the analysis in steps 1 and 2 above, further testing is needed to assess long-term repeated dose toxicity, the test methods described further below should be used. In addition to the test methods mentioned below, new OECD validated tests for repeated dose toxicity should be taken into account once available in deciding the test strategy. The OECD Test Guideline programme as well as non-animal test methods that undergo validation available by ECVAM should be regularly consulted for any updates.

The results of the long-term studies conducted and reported, taken together with other relevant data and information on the active substance, should be sufficient to permit the identification of effects, following repeated exposure to the active substance, and in particular should be sufficient to:

- identify adverse effects resulting from long-term exposure to the active substance;
- identify target organs, where relevant;
- establish the dose-response relationship and mode of action;
- establish the NOAEL and, if necessary, other appropriate reference points.

Correspondingly, the results of the carcinogenicity studies taken together with other relevant data and information on the active substance, should be sufficient to permit the evaluation of hazards for humans, following repeated exposure to the active substance, to be assessed, and in particular should be sufficient:

(a) to identify carcinogenic effects resulting from long-term exposure to the active substance;
(b) to establish the species, sex, and organ specificity of tumours induced;
(c) to establish the dose-response relationship and mode of action;
(d) where possible, to identify the maximum dose eliciting no carcinogenic effect;
(e) where possible, to determine the mode of action and human relevance of any identified carcinogenic response.

If comparative metabolism data indicate that either rat or mouse is an inappropriate model for human cancer risk assessment, an alternative species should be considered.

Experimental data, including the elucidation of the possible mode of action involved and relevance to humans, should be provided where the mode of action for carcinogenicity is considered to be non-genotoxic. Suitable mode of action (MOA) studies can be considered to confirm non-relevance of the non-genotoxic MOA to humans.

Investigation of toxicokinetic parameters generated within the combined long term toxicity study should also be considered as described also for short-term toxicity studies in Chapter II Section 8.9.2.

The following test methods should be used.

Test methods for long-term repeated dose toxicity:

- EC method B.30 Chronic toxicity test.
- EC method B.33 Combined chronic toxicity/carcinogenicity test.
- OECD Test Guideline 452: Chronic Toxicity Studies.
- OECD Test Guideline 453: Combined Chronic Toxicity/Carcinogenicity Studies.

8.9.4. Further repeated dose studies (ADS)

When the available data are inadequate for hazard characterisation and risk assessment, further repeated dose studies should be undertaken, including testing on a second species (non-rodent), studies of longer duration than the studies already available or through a different route of administration. However, testing should not be initiated before the evaluating competent authority has indicated that further testing is necessary. The decision on further testing should be based on expert judgement and on a case-by-case basis.

Requiring further repeated dose toxicity studies
Further repeated dose studies including testing on a second species (non-rodent), studies of longer duration or through a different route of administration shall be undertaken in cases of:

- *no other information on toxicity for a second species (non-rodent) is provided for,*

  When all the toxicological data concern rodent species, an assessment of the data needs to be performed to understand if testing with another species is likely to provide additional information (e.g. potential of different mode of action within different species).

  or

- *failure to identify a no observed adverse effect level (NOAEL) in the 28- or the 90-day study, unless the reason is that no effects have been observed at the limit dose,*

  This trigger is not considered if no effects were observed at the limit dose. Furthermore, failing to identify a NOAEL should not trigger additional studies by default. If the data are sufficient for a robust hazard assessment and for Classification and Labelling, the LOAEL may be used as the starting point.

  or
- *substances bearing positive structural alerts for effects for which the rat or mouse is an inappropriate or insensitive model,*

  A study protocol will be identified that can be reliably performed in a more suitable animal species. It is however possible to conclude that the structural alert concerns an effect that is specific to humans and/or none of the animal models is suitable for studying this specific effect. In this case all the available information, including scientific literature and human data, will be taken into account to judge whether the risk to humans can be concluded. The human data may consist of e.g. records of worker/consumer experience, case reports, consumer tests or epidemiological studies. Whether further testing will be required will depend on a case-by-case expert judgment.

  or
- *toxicity of particular concern (e.g. serious/severe effects),*

  If toxicity of particular concern is already established, the substance will be classified accordingly and the appropriate risk management measures will be implemented, and therefore no further testing is required.

  or
- *indications of an effect for which the available data is inadequate for toxicological and/or risk characterisation. In such cases it may also be more appropriate to perform specific toxicological studies that are designed to investigate these effects (e.g. immunotoxicity, neurotoxicity, hormonal activity),*

  In some cases data derived by protocols designed for other endpoints, as for example the OECD Test Guideline 443 (Extended One-Generation Reproductive Toxicity Study) may provide valuable information on specific effects such as immunotoxicity, neurotoxicity or endocrine disruption. Furthermore, where a need is identified for a modification in the study protocol to cover specific needs, this will be done in consultation with the evaluating competent authority. Only in exceptional cases should non-standard protocols be used because the scientific value of such results can be questioned.

  or
- *concern regarding local effects for which a risk characterisation cannot be performed by route-to-route extrapolation,*

  A new repeated dose toxicity study for the purpose of performing quantitative risk characterisation for local effects should not be performed by default due to the difficulty in deriving threshold levels for local effects that are also relevant for humans. The benefit from the generation of additional data for this purpose should be considered against the effectiveness of qualitative risk characterisation as another option for ensuring safe use.

or

- *particular concern regarding exposure (e.g. use in biocidal products leading to exposure levels which are close to the toxicologically relevant dose levels),*

  Further studies might be necessary e.g. when the biocidal product is used in one or more consumer products and the (combined) exposure levels are close to toxicologically relevant dose levels where effects on humans may be expected in the relevant time frame. Any exposure-triggered studies proposed or required should be considered on a case-by-case basis.

or

- *effects shown in substances with a clear relationship in molecular structure with the substance being studied were not detected in the 28- or the 90-day study,*

  The study protocol and the conditions in which the effects were seen in another substance will be examined in detail in order to identify the conditions in which the effect would be expected to occur for the substance to be studied. The study protocol will be selected to repeat and possibly extend the conditions where the effect has been observed. However, where applicable, mechanistic *in vitro* studies examining the specific mechanism of action of the related substances should have preference over further animal studies.

or

- *the route of administration used in the initial repeated dose study was inappropriate in relation to the expected route of human exposure and route-to-route extrapolation cannot be made.*

  The possibility of route-to-route extrapolation should be carefully considered before concluding that it is not appropriate taking into account the toxicokinetic information available and the use of modelling approaches when performing route-to-route extrapolation.

8.10. Reproductive toxicity

For evaluation of consumer safety of active substances that may end up in food or feed, it is necessary to conduct toxicity studies by the oral route

Possible effects on reproductive physiology and the development of progeny should be investigated and reported concerning the following aspects:

- Impairment of male and female reproductive functions or capacity, for example from effects on oestrus cycle, sexual behaviour, any aspect of spermatogenesis or oogenesis, or hormonal activity or physiological response which would interfere with the capacity to fertilise, fertilisation itself or development of the fertilised ovum up to and including implantation.
- Adverse effects on the progeny, for example any effect interfering with normal development, both before and after birth. This includes morphological anomalies such as changes in anogenital index, nipple retention, and functional disturbances (such as reproductive and neurological effects).

Effects accentuated over generations should be reported.

Steps 1 and 2 Collection and evaluation of available information

For the assessment of existing information (non-human data: physicochemical properties, grouping, (Q)SARs and expert systems, *in vitro* data; human data and animal data) further guidance is available within the Guidance on the Application of the CLP Criteria (ECHA, 2012a) and Part B Human Health Effects Assessment (BPR guidance under development).

The studies need not be conducted if:

- *the substance is known to be a genotoxic carcinogen and appropriate risk management measures are implemented including measures related to reproductive toxicity; or*
- *the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented including measures related to reproductive toxicity; or*
- *the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available provided that the dataset is sufficiently comprehensive and informative), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure, e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and the pattern of use indicates there is no or no significant human exposure*
- *a substance is known to have an adverse effect on fertility, meeting the criteria for classification as Reproductive toxicity Cat 1A or 1B: May damage fertility (H360F), and the available data are adequate to support a robust risk assessment, then no further testing for fertility will be necessary. However, testing for development toxicity must be considered*
- *a substance is known to cause developmental toxicity, meeting the criteria for classification as Reproductive toxicity Cat 1A or 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, then no further testing for developmental toxicity will be necessary. However, testing for effects on fertility must be considered*

Step 3 Generation of new test data
If after the analysis in steps 1 and 2 above, further testing is needed to assess reproductive toxicity, the test methods described further below (Chapter II Section 8.10.1-8.10.3) should be used. In addition to the test methods mentioned below, new OECD validated tests for reproductive toxicity should be taken into account once available in deciding the test strategy. The OECD Test Guideline programme as well as non-animal test methods that undergo validation available by ECVAM should be regularly consulted for any updates.

8.10.1. Pre-natal developmental toxicity study, preferred species is rabbit; oral route of administration is the preferred route.

The study shall be initially performed on one species

The developmental toxicity studies reported, taken together with other relevant data and information on the active substance, should be sufficient to permit the assessment of effects on embryonic and foetal development, following repeated exposure to the active substance, and in particular should be sufficient:

(a) to identify direct and indirect effects on embryonic and foetal development resulting from exposure to the active substance;
(b) to identify any maternal toxicity;
(c) to establish the relationship between observed responses and dose in both dam and offspring;
(d) to establish NOAELs for maternal toxicity and pup development;

(e) to provide additional information on adverse effects in pregnant as compared with non-pregnant females;
(f) to provide additional information on any enhancement of general toxic effects of pregnant animals.

Developmental toxicity should be determined in rabbits by the oral route. The decision on species to be tested primarily depends on consideration of all available information including the type of substance to be tested.

Malformations and variations and external skeletal and visceral anomalies should be reported separately and combined in such a way that all relevant changes which are observed to occur in characteristic patterns in individual foetuses or those that can be considered to represent different grades of severity of the same type of change are reported in a concise manner.

Diagnostic criteria for malformations and variations should be given in the report. The terminology should follow that presented in OECD Guidance Document 43 Appendix I (OECD, 2008b) and via the DevTox project (http://www.devtox.org).

Further guidance on conditions for historical control data is provided in OECD Guidance Document 43 (OECD, 2008b).

When indicated by observations in other studies or the mode of action of the test substance, supplementary studies or information may be required to provide information on the postnatal manifestation of effects such as developmental neurotoxicity.

The following test methods for pre-natal developmental toxicity should be used:
- EC method B.31 Prenatal developmental toxicity study.
- OECD Test Guideline 414: Prenatal developmental toxicity study.
- OECD Test Guideline 426: Developmental neurotoxicity study.

8.10.2. Two-generation reproductive toxicity study, rat, oral route of administration is the preferred route.

If another reproductive toxicity test is used justification shall be provided. The extended one-generation reproductive toxicity study adopted at OECD level shall be considered as an alternative approach to the multi-generation study

Investigations should take account of all available and relevant data, including the results of general toxicity studies if relevant parameters (such as semen analysis, oestrous cyclicity, reproductive organ histopathology) are included, as well as knowledge concerning structural analogues to the active substance.

The active substance and its relevant metabolites should be measured in milk, although not required in the OECD test guideline, as a second tier investigation where relevant effects are observed in the offspring or are expected (for example from a range-finding study).

Potential neurotoxic, immunotoxic effects and effects potentially related to changes in the hormonal system should be carefully addressed and reported.

In order to provide useful information in the design and interpretation of developmental toxicity studies, information on blood concentration of the active substance in parents and foetus/offspring may be included in higher tier studies and reported.

The reproductive toxicity studies reported, taken together with other relevant data and information on the active substance, should be sufficient to permit the identification of effects for reproduction, following repeated exposure to the active substance, and in particular should be sufficient to:

(a) identify direct and indirect effects on reproduction resulting from exposure to the active substance;
(b) identify any non-reproductive adverse effects occurring at lower doses than in short-term and chronic toxicity testing;
(c) establish the NOAELs for parental toxicity, reproductive outcome and pup development.

The OECD extended one-generation reproductive toxicity study (OECD TG 443) can be considered as an alternative approach to the multi-generation study. The OECD TG 443 is a modular flexible study design and thus the study design and investigational details should be defined and agreed with the evaluating competent authority to assure that the relevant aspects are taken into consideration.

The decision on whether or not to mate the F1B animals to produce the F2 within the extended one-generation reproductive toxicity study should be made on a case-by-case basis taking into account substance specific properties and remaining uncertainty from the omission of the mating of F1B animals and production of F2 offspring that may have impact in hazard identification and characterisation. Information from similar substances, use of the substance and the exposure conditions may support the decision making on the assessment of the reproductive performance of the F1 animals and effects in F2 generation.

Similarly the decision on inclusion of the developmental neurotoxicity and the developmental immunotoxicity cohorts within the OECD extended one-generation reproductive toxicity test, should be made taking into account all available information with regard to neurotoxicity and immunotoxicity potential of the substance as derived by existing data (e.g. repeated dose toxicity studies performed with the substance or similar substances), non-test data (e.g. structural alerts by expert systems). In the absence of any existing information or alerts, in order to account for any remaining uncertainty it would be preferred that the two cohorts were performed within the test. In addition the use pattern of the substance and exposure conditions may support the decision on whether one or both of these cohorts should be conducted in order to reduce the remaining uncertainty of detecting potential triggers for (developmental) neurotoxicity and/or (developmental) immunotoxicity.

Where necessary for a better interpretation of the effects on reproduction and as far as this information is not yet available, supplementary studies may be required to provide information on the affected gender and the possible mechanisms.

The following test methods for generation reproductive toxicity should be considered:

- EC method B.35 Two-generation reproduction toxicity study.
- OECD Test Guideline 416: Two-Generation Reproduction Toxicity.
- OECD Test Guideline 443: Extended One-generation Reproduction Toxicity.

8.10.3. Further pre-natal developmental toxicity study, preferred species is rat, oral route of administration (ADS)

A decision on the need to perform additional studies on a second species or mechanistic studies should be based on the outcome of the first test (8.10.1) and all other relevant available data (in particular rodent reprotox studies).

The assessment of this endpoint should be carried out according to the EC method B.31 or the corresponding OECD Test Guideline 414 for Prenatal developmental toxicity study. Further guidance is also available in OECD Guidance Document 43 (OECD, 2008b); Guidance on the Application of the CLP Criteria (ECHA, 2012a).

A decision on the need to perform additional studies on a second species (rat) or mechanistic studies should be based on the outcome of the first test (Chapter II Section 8.10.1) and all other relevant data. The decision on species to be tested primarily depends on consideration of all available information including the type of substance to be tested.

Besides the results from the pre-natal developmental toxicity study all other relevant and available data including indications from repeat dose toxicity studies (28-day and /or 90-day studies), ADME, multigeneration-, developmental neurotoxicity- or the extended one-generation study, further neurotoxicity studies and, if possible, the mode of action of the test substance should be considered when deciding for an additional pre-natal developmental toxicity study on a second species. Knowledge of structural analogues to the active substance should also be included in the assessment. A second pre-natal developmental toxicity study on another species (rat) does not need to be performed if no prenatal developmental effects are observed in the study conducted in the first species and if no indication of pre- and/or postnatal developmental toxicity are observed in one- or multigeneration reproductive toxicity study (performed in the rat) are observed at the highest dose tested.

According to Janer et al (Janer, et al., 2008) the rat and the rabbit show similar sensitivity with regard to detecting developmental toxicity.

When in specific cases further examination of developmental toxicity is required, in addition to the test performed in the first species (rabbit) this should be done with a focus on elucidating the mode of action of the substance and relevance of the effects for humans. It is more likely that such investigations would require rather mechanistic studies than a new pre-natal developmental toxicity test.

8.11. Carcinogenicity

The carcinogenicity study identifies the carcinogenicity potential of the substance in laboratory animals in order to facilitate the extrapolation of potential risks to humans. The studies should be sufficient to establish the species specificity and organ specificity of tumours induced, to establish the dose-response relationship and for non-genotoxic carcinogens to identify doses eliciting no adverse effects (threshold dose).

See 8.11.1 for new study requirements

Steps 1 and 2
For the assessment of existing information (non-human data: physicochemical properties, grouping, (Q)SARs and expert systems, *in vitro* data; human data and animal data) further guidance is available within the Guidance on the Application of the CLP Criteria (ECHA, 2012a) and Part B Human Health Effects Assessment (BPR guidance under development).

A carcinogenicity study does not need to be conducted if:

- *the substance is classified as mutagen category 1A or 1B. The default presumption would be that a genotoxic mechanism for carcinogenicity is likely. In these cases, a carcinogenicity test will normally not be required.*

In addition the study does not need to be conducted if:

- *No genotoxic potential for humans is identified in genotoxicity tests, and*
- *Possible mechanisms of toxicological effects observed in subchronic toxicity studies are without any indications of non-genotoxic carcinogenicity and there are no structural alerts for carcinogenicity, and*
- *The subchronic studies in rodents and/or non-rodents are without indication of substance related adverse effects at the limit dose level.*

8.11.1. Combined carcinogenicity study and long-term repeated dose toxicity

Rat, oral route of administration is the preferred route. If an alternative route is proposed a justification must be provided.

See Chapter II Section 8.9.3.

8.11.2. Carcinogenicity testing in a second species

- *A second carcinogenicity study should normally be conducted using the mouse as test species*
- *For evaluation of consumer safety of active substances that may end up in food or feed, it is necessary to conduct toxicity studies by the oral route*

The rat and the mouse are usually the species used for testing carcinogenic potential, while the rat is used for a combined chronic toxicity/ carcinogenicity testing.

The study is not needed if the conditions specified in 8.11 are fulfilled. In principle a second study in another rodent species is not likely to provide additional information as according to Billington et al (Billington, et al., 2010) the mouse carcinogenicity study does not provide additional information when results from carcinogenicity studies with rat and mice have been compared.

For the purpose of elucidating the mode of action and human relevance when needed further investigation of carcinogenicity after obtaining the results of the combined chronic toxicity study should be considered on a case-by-case basis giving priority to the performance of mechanistic studies.

8.12. Relevant health data, observations and treatments

Justification should be provided if data is not available.

When there are no human studies/data already available, new human studies should not be conducted.

Data and information on the effects of human exposure may provide valuable information for confirming the validity of extrapolations made and conclusions reached from animal data and for identifying unexpected adverse effects which are specific to humans.

Available data and information of adequate quality following accidental or occupational exposure have to be submitted.

8.12.1. Medical surveillance data on manufacturing plant personnel

The reports should include detailed information on the design of the programme and exposure to the active substance and to other chemicals.

Data relevant to the mechanism of the action of substance should also be included where feasible. The data may consist of published articles or unpublished medical surveys.

8.12.2. Direct observation, e.g. clinical cases, poisoning incidents

Practical data and information relevant to the recognition of the symptoms of poisoning, on the effectiveness of first aid and therapeutic measures must be included.

The reports should include a complete description of the exposure situation, clinical symptoms observed and therapeutic measures.

Reports of any follow-up studies should be enclosed.

8.12.3. Health records, both from industry and any other available sources

8.12.4. Epidemiological studies on the general population

Information related to occupational exposure or other exposure is available from three main sources: case reports, descriptive epidemiological studies and analytical epidemiological studies, case-control or cohort studies.

Where available, data should be supported with data on levels and duration of exposure.

8.12.5. Diagnosis of poisoning including specific signs of poisoning and clinical tests

A detailed description of clinical signs and details of clinical tests useful for diagnostic purposes (bio-monitoring) must be included.

Symptoms of poisoning including full details of the time courses involved to all exposure routes must be described.

8.12.6. Sensitisation/allergenicity observations

Information on the sensitisation/allergenicity of workers and others exposed must be provided and included, and where relevant, any incidence of hypersensitivity.

Reports should include details of frequency, level, duration, symptoms observed, size of exposure population and other relevant data.

Evidence that the substance can induce specific respiratory hypersensitivity will usually be based on human experience data. The clinical history data including both medical and occupational history, and reports from appropriate lung functions tests related to exposure to the substance should be submitted, if available. Reports of other supportive evidence must also be submitted, e.g.:

(a) a chemical structure related to substances known to cause respiratory hyper-sensitivity,
(b) *in vivo* immunological tests,
(c) *in vitro* immunological tests,
(d) studies indicating other specific but non-immunological mechanisms of action, or
(e) data from a positive bronchial challenge test.

8.12.7. Specific treatment in case of an accident or poisoning: first aid measures, antidotes and medical treatment, if known

First aid measures in the event of poisoning and eye contamination must be provided.

Therapeutic regimes and the use of antidotes must be described. Information based on practical experience, where it exists and is available, or in other cases information based on theoretical grounds, as to the effectiveness of alternative treatment regimes, where relevant must be provided. Contraindications associated with particular regimes, particularly those relating to 'general medical problems' and conditions, must be described.

8.12.8. Prognosis following poisoning

The expected effects and the duration of these effects following poisoning must be described.

8.13. Additional studies (ADS)

Additional data, which may be required depending on the characteristics and intended use of the active substance

Other available data: Available data from emerging methods and models, including toxicity pathway-based risk assessment, in vitro and 'omic' (genomic, proteomic, metabolomic, etc.) studies, systems biology, computational toxicology, bioinformatics, and high throughput screening shall be submitted in parallel

Toxicity studies of metabolites
Supplementary studies, where they relate to substances other than the active substance, are not a routine requirement. Decisions as to the need for supplementary studies should be made on a case-by-case basis.

Where as a result of metabolism or other processes, metabolites from plants or in animal products, soil, groundwater, open air differ from those in animals used for the toxicology studies or are detected in low proportions in animals, further testing should be carried out on a case-by-case basis, taking into account the amount of metabolite and the chemical structure of the metabolite compared to the parent.

Supplementary studies on the active substance
Supplementary studies should be carried out where they are necessary to further clarify observed effects taking into account the results of the available toxicological and metabolism studies and the most important exposure routes. Such studies may include:

(a) studies on absorption, distribution, excretion and metabolism, in a second species;
(b) studies on the immunotoxicological potential;
(c) a targeted single dose study to derive appropriate acute reference values (ARfD, AEL);
(d) studies on other routes of administration;
(e) studies on the carcinogenic potential;
(f) studies on mixture effects.

Studies required should be designed on an individual basis, in the light of the particular parameters to be investigated and the objectives to be achieved.

8.13.1. Phototoxicity - additional study (ADS)

The study should provide information on the potential of certain active substances to induce cytotoxicity in combination with light, for example active substances that are phototoxic *in vivo* after systemic exposure and distribution to the skin, as well as active substances that act as photoirritants/photosensitisers after dermal application to the skin. A positive result should be taken into account when considering potential human exposure. For photomutagenicity see also Chapter II Section 8.6 also. The *in vitro* study should be required only where the active substance absorbs electromagnetic radiation in the range 290-700 nm and is liable to reach the eyes or light-exposed areas of skin, either by direct contact or through systemic distribution.

If the ultraviolet/visible molar/extinction/absorption coefficient of the active substance is less than 10L x mol^{-1} x cm^{-1}, no toxicity testing is required.

The following test methods should be used.

Test methods for phototoxicity:

- EC method B.41.
- OECD Test Guideline 432: *In vitro* 3T3 NRU phototoxicity test.

8.13.2. Neurotoxicity including developmental neurotoxicity (ADS)

- *The preferred test species is the rat unless another test species is justified to be more appropriate*
- *For delayed neurotoxicity tests the preferred species will be the adult hen*
- *If anticholinesterase activity is detected a test for response to reactivating agents should be considered*

If the active substance is an organophosphorus compound or if there is any evidence e.g. knowledge of the mechanism of action or from repeated dose studies that the active substance may have neurotoxic or developmental neurotoxic properties then additional information or specific studies will be required.

For evaluation of consumer safety of active substances that may end up in food or feed, it is necessary to conduct toxicity studies by the oral route

Such studies should be performed for active substances with structures that are similar or related to those capable of inducing neurotoxicity, and for active substances which induce specific indications of potential neurotoxicity, neurological signs or neuropathological lesions in toxicity studies at dose levels not associated with marked general toxicity. Performance of such studies should also be considered for substances with a neurotoxic mode of action. Neurotoxicity studies detect functional changes and/or structural and biochemical changes in the central and peripheral nervous systems. These changes can be morphological, physiological (e.g. electroencephalographic changes), or behavioural nature, or can be changes in biochemical parameters (e.g. neurotransmitter levels).

Indications of neurotoxicity can be acquired from the standard systemic toxicity studies. Further investigation is possible using standard repeated dose toxicity tests (such as 28- and 90 day repeated dose toxicity studies or the extended one generation test) with incorporation of specific neurotoxicity measures.

Neurotoxicity studies in rodents should provide sufficient data to evaluate the potential neurotoxicity of the active substance (neurobehavioural and neuropathological effects) after single and repeated exposure.

Steps 1 and 2 Collection and evaluation of available information
For the assessment of existing information (non-human data: physicochemical properties, grouping, (Q)SARs and expert systems, *in vitro* data; human data and animal data) further guidance is available within the Guidance on the Application of the CLP Criteria (ECHA, 2012a) and Part B Human Health Effects Assessment (BPR guidance under development).

Step 3 Generation of new test data
When it is considered necessary to conduct a study to investigate specific organ/system toxicity, it is important that the study design is discussed by the contractor/laboratory and the assessor, paying particular attention to the protocol to be used, before initiating the study. The need for (and scope/size of) studies using live animals should be particularly carefully considered.

If further standard 28- or 90-day studies are to be conducted, a number of nervous system endpoints will be examined. These endpoints should be included in the tests irrespective of the administration route. A standard study with additional parameters could be considered. In some cases, it may be necessary to conduct a specific study such as a neurotoxicity test using the OECD Test Guideline 424 (Neurotoxicity Study in Rodents) or corresponding EC method B.43 (Neurotoxicity Study in Rodents) with possible inclusion of a satellite group for assessment of reversibility of effects. The OECD Test Guideline 424 is intended for confirmation or further characterisation of potential neurotoxicity identified in previous studies. The OECD Guideline allows for a flexible approach, in which the number of simple endpoints which duplicate those already examined during standard testing may be minimised, and where more effort is put into in-depth investigation of more specific endpoints by inclusion of more specialised tests. Adjustment of dose levels to avoid confounding by general toxicity should be considered.

If data from standard toxicity studies are clearly indicative of specific neurotoxicity, e.g. neurotoxicity occurring at lower dose levels than systemic toxicity, further specific neurotoxicity testing is required to confirm and extend the findings from the general toxicity studies and to establish an NOAEL for neurotoxicity. Again, the neurotoxicity test according to OECD Test Guideline 424 is considered appropriate for this situation.

Standard exposure conditions may not always be adequate for neurotoxicity studies. The duration of exposure needed to induce specific neurotoxic effects in an animal experiment will depend on the underlying mechanism of action. Short-term peak exposures can be important for certain types of substance/effect. When the test compound is administered as a bolus via the intravenous, subcutaneous or oral route it is essential to determine the time-effect course, and to perform measurements of neurotoxicity parameters preferentially at the time of peak effect.

For example, the neurotoxicity associated with short-term exposure to some volatile organic solvents has largely been identified following human exposure - particularly occupational exposure. Acute inhalation studies, using protocols designed to detect the expected effects, are ideal for such substances/effects. For some neurotoxic substances a long exposure period is necessary to elicit neurotoxicity.

In addition in exceptional cases when relevant triggers are met testing for developmental neurotoxicity effects should be considered. Relevant triggers could be if the substance has been shown to (1) cause structural abnormalities of the central nervous system, (2) cause clear signs of behavioural or functional adverse effects of nervous system involvement in adult studies e.g. repeated-dose toxicity studies or (3) have a mode of action that has been closely linked to

neurotoxic or developmental neurotoxicity effects e.g. cholinesterase inhibition or thyroid effects. However, in the case of (3) targeted testing on the specific mode of action in developing animals may provide sufficient information for regulatory purposes.

The DNT test protocol (OECD TG 426, developmental neurotoxicity) is designed to be performed as an independent study. However, observations and measurements described in the protocol can also be added on to a generation reproduction study. However, when the developmental neurotoxicity study is incorporated within or attached to another study, it is imperative to preserve the integrity of both study types. It should also be taken into consideration that by incorporating the developmental neurotoxicity investigations into other studies, it may not be possible to investigate as many parameters with similar statistical power than in an independent study such as the OECD TG 426.

The most appropriate methods for further investigation of neurotoxicity should be determined on a case-by-case basis, guided by the effects seen in the standard systemic toxicity tests and/or from SAR-based predictions. Extensive coverage of methods which may be used is given in (OECD, 2004b), (WHO, 1986) and (ECETOC, 1992), and some are summarised in Table 3, below.

Table 3 Methods for investigation of neurotoxicity

Effect	Methods available	References *
Morphological changes	Neuropathology. Gross anatomical techniques. Immunocytochemistry. Special stains.	Krinke, 1989; O'Donoghue, 1989; Mattsson et al., 1990
Physiological changes	Electrophysiology (e.g. nerve conduction velocity (NCV), Electroencephalogram (EEG), evoked potentials).	Fox et al., 1982; Rebert, 1983; Mattsson and Albee, 1988
Behavioural changes	Functional observations. Sensory function tests. Motor function tests (e.g. locomotor activity). Cognitive function tests.	Robbins, 1977; Tilson et al., 1980; Cabe and Eckerman, 1982; Pryor et al., 1983; Moser and McPhail, 1990; Moser, 1995
Biochemical changes	Neurotransmitter analyses. Enzyme/protein activity. Measures of cell integrity.	Dewar and Moffett, 1977; Damstra and Bondy, 1982; Cooper et al., 1986; Costa, 1998

* Given in full in ECETOC (1992), WHO (1986) or Mitchell (1982) in the References.

If significant acetylcholine esterase inhibition is detected, a test for response to reactivating agents should be considered. Available guidance on the setting of acute reference dose (ARfD) for pesticides from JMPR should also be considered.

If the active substance is an organophosphorus compound or if there is any evidence e.g. knowledge of the mechanism of action or from repeat dose studies that the active substance may have neurotoxic or developmental neurotoxic properties then additional information or specific studies will be required.

Delayed polyneuropathy studies

Delayed polyneuropathy studies should provide sufficient data to evaluate if the active substance may provoke delayed polyneuropathy after acute and repeated exposure. A repeated exposure study may be waived unless there are indications that the compound accumulates and significant

inhibition of neuropathy target esterase or clinical/histopathological signs of delayed polyneuropathy occur at around the hen LD_{50} as determined in the single dose test.

These studies should be performed for active substances of similar or related structures to those capable of inducing delayed polyneuropathy such as organophosphorus compounds.

For organophosphorus compounds and carbamates, delayed neurotoxicity tests in the laying hen after acute and repeated exposure (OECD TG 418 and OECD TG 419) should be performed.

Test methods for delayed neuropathy:

- EC method B.43 Neurotoxicity study in rodents
- OECD Test Guideline 424: Neurotoxicity study in rodents. EC method B.37 Delayed neurotoxicity of organophosphorus substances after acute exposure
- EC method B.38 Delayed neurotoxicity of organophosphorus substances 28-day repeated dose study
- OECD Test Guideline 419: Delayed Neurotoxicity of Organophosphorus Substances: 28-day Repeated Dose Study
- OECD Test Guideline 418: Delayed Neurotoxicity of Organophosphorus Substances Following Acute Exposure. Developmental Neurotoxicity
- OECD Test Guideline 426: Developmental Neurotoxicity study
- OECD Test Guideline 443: Extended one generation reproductive study

8.13.3. Endocrine disruption (ADS)

If there is any evidence from in vitro, repeated dose or reproduction toxicity studies, that the active substance may have endocrine disrupting properties, additional information or specific studies shall be required to:

- *elucidate the mode/mechanism of action*
- *provide sufficient evidence for relevant adverse effects*

For evaluation of consumer safety of active substances that may end up in food or feed, it is necessary to conduct toxicity studies by the oral route

Information to be generated with regard to elucidating the endocrine mode of action should take into account the design of *in vivo* toxicity studies (repeated dose toxicity, extended one generation toxicity study) to ensure that specific parameters linked to endocrine properties of an active substance are investigated when conducted in *in vivo* animal tests. In addition information derived from the use of expert systems that indicate structural similarities to known endocrine disrupters should be taken into account in deciding the need for additional testing.

Studies required should be designed on an individual basis and taking into account Union or internationally agreed guidelines, in the light of the particular parameters to be investigated and the objectives to be achieved. Expert judgment is needed to decide whether there is a need to perform additional tests or whether the existing information can be used to conclude that the substance is an endocrine disruptor.

OECD Test Guideline protocols for the examination of endocrine disruption as well as Guidance on this topic by the Commission and OECD should be considered to decide on the design of tests to examine the potential of endocrine disruption for active substances.

8.13.4. Immunotoxicity including developmental immunotoxicity (ADS)

If there is any evidence, from skin sensitisation, repeated dose or reproduction toxicity studies, that the active substance may have immunotoxic properties then additional information or specific studies shall be required to:

- *elucidate the mode/mechanism of action*
- *provide sufficient evidence for relevant adverse effects in humans*

For evaluation of consumer safety of active substances that may end up in food or feed, it is necessary to conduct toxicity studies by the oral route

The objectives of investigating immunotoxicity are to investigate:
- *whether the substance of interest has the potential to induce adverse effects involving the immune system; special attention should be paid to the adverse immunotoxic outcome among susceptible and vulnerable groups;*
- *the adverse outcomes caused by exposure to the substance (inflammation, immunosuppression; increased propensity for allergic disease; hypersensitivity reactions directed to the chemical itself; increased risk of autoimmune disease; dysfunctional responses resulting in tissue or organ damage or dysfunction; impact on the developing immune system);*

Steps 1 and 2 Collection and evaluation of available information
For the assessment of existing information (non-human data: physicochemical properties, grouping, (Q)SARs and expert systems, *in vitro* data; human data and animal data) further guidance is available within the Guidance on the Application of the CLP Criteria (ECHA, 2012a) and Part B Human Health Effects Assessment (BPR guidance under development).

The guidance for the evaluation of all available information before conducting new tests is available in Part B Effects Assessment (BPR guidance under development) and is largely based on the WHO/IPCS Guidance on Immunotoxicity for Risk Assessment (WHO, 2012).

It has also to be noted that current animal studies provide information from an unchallenged immune system which has potential pitfalls in the assessment of immunotoxic potential (WHO/IPCS guidance for Immunotoxicty risk assessment for chemicals (WHO, 2012)).

Step 3 Generation of new test data
If immunotoxicity potential is identified tests consisting of a more specific confirmatory set of studies or in-depth mechanistic studies, is carried out to confirm and further characterize the endpoint. It is worth noting that further testing to investigate immune function should be conducted only if the outcomes of such studies can be interpreted in relation to the risk assessment for the substance of interest. In addition, the need for further testing to characterise effects of concern for immunotoxicity has to be considered on a case-by-case basis.

It should be considered that the conduct of the repeated dose toxicity tests and the reproductive toxicity tests should be performed in a way that allows evaluation of immunotoxicity potential (e.g. Repeated dose toxicity according to US EPA OPPTS 870.7800 (Health Effects Test Guidelines Immunotoxicity) including parameters for immunotoxicity and OECD TG 443 -extended one generation toxicity test- may be conducted with the immunotoxicity cohort).

The test methods to be used for further immunotoxicity studies will depend also on the triggers from steps 1 and 2 of the weight of evidence analysis. Different test methods can be employed for

assessing immune suppression, immune stimulation and autoimmunity as well as developmental immunotoxicity.

Reviews of principles and methods for immunotoxicity are available from WHO/IPCS:

- WHO/IPCS Environmental Health Criteria (EHC) 180, Principles and Methods for Assessing Direct Immunotoxicity Associated with Exposure to Chemicals (WHO, 1996)
- WHO/IPCS Environmental Health Criteria (EHC) 212, Principles and Methods for Assessing Allergic Hypersensitization Associated with Exposure to Chemicals (WHO, 1999)
- WHO/IPCS Environmental Health Criteria (EHC) 236, Principles and Methods for Assessing Autoimmunity Associated with Exposure to Chemicals (WHO, 2007)
- WHO/IPCS Guidance for immunotoxicity risk assessment for chemicals, Harmonisation project document No 10 (WHO, 2012)

Below a list of methods that can be considered for further immunotoxicity testing is provided. This list is not exhaustive but provides the methodological aspects to consider on a case-by-case basis.

Immune Suppression

- US EPA OPPTS 870.7800 Health Effects Test Guidelines Immunotoxicity
- Functional studies as described under Additional Immunotoxicity Studies below

Immune stimulation including hypersensitivity (skin and respiratory sensitisation)

- LLNA assay (see sensitisation section)
- Functional studies as described under Additional Immunotoxicity Studies below

Autoimmunity

- Functional studies as described under Additional Immunotoxicity Studies below

Developmental Immunotoxicity

- OECD Test Guideline 443: Extended One-Generation Reproductive Toxicity Study

Additional Immunotoxicity Studies (adopted from ICH S8)

- T-cell Dependent Antibody Response (TDAR)
- Immunophenotyping
- Natural Killer Cell Activity Assays
- Host Resistance Studies
- Macrophage/Neutrophil Function
- Assays to Measure Cell-Mediated Immunity

8.13.5. Mechanistic data - any studies necessary to clarify effects reported in toxicity studies (ADS)

This data may be relevant on the basis of the toxicological properties of a substance and can clarify the mode of action of the chemical. In addition, this can provide information for refinement in the evaluation process for mixtures.

Studies of the mechanisms of toxicity/mode of action may be necessary when there are indications that active substance may have e.g. a non-genotoxic mechanism for carcinogenicity, species specific effects, adverse effects on reproduction, immunotoxicity or hormone related effects. Such studies are important in confirming that effects observed in experimental animals may be of limited or no relevance to humans.

8.14. Studies related to the exposure of humans to the active substance (ADS)

Toxicity of degradation products, by-products and reaction products related to human exposure.

Information is required on the toxic effects of substances generated from an active substance, other than mammalian metabolites, in normal use of biocidal product.

The decision as to the need for these data should be made on a case-by-case basis by expert judgment. Where human exposure is significant, toxicity testing may be needed.

These data may be relevant for many product-types for example: product-types 1 and 2 (reaction products with water when the substance is used for human hygiene purposes or reaction products with water or other materials released in water or air when the substance is used for the treatment of bathing waters), product-type 5 (substances produced in a reaction with drinking water), product-types 6, 7, 9 and 10 (residuals in treated materials), product-type 8 (irritating and sensitising effects of chemical compounds, such as metal salts, developed on the surface of the treated wood) and product-type 18 (products, which may produce harmful substances with water during gassing).

8.15. Toxic effects on livestock and pets (ADS)

An estimation of toxic effects and exposure via different exposure routes (e.g. inhalation, licking, skin contact and ingestion of poisoned bait) and in relevant, but exceptional cases, toxicity testing in livestock and pets is required. Toxic effects for livestock and pets should be estimated or studied if the substance is to be used in spaces in which animals are housed, kept or transported or exposure is possible via drinking water or feeding stuffs. Information on lethal doses for different species, symptoms of poisoning, details of the time courses in case of poisoning and antidotes should also be submitted, if available.

These data may be relevant e.g. for product-type 3 (substances used for veterinary hygiene purposes), product-type 4 (disinfection of surfaces and equipment), product-type 5 (drinking water) product-types 8 and 10 (treated materials in areas in which animals are housed, kept or transported), product-types 14, 15 and 23 (ingestion of baits), product-types 16 and 17 (contaminated drinking water), product-types 18 and 19 (repellents to be used for veterinary hygiene purposes, residential indoor use).

8.16. Food and feeding stuffs studies including for food producing animals and their products (milk, eggs and honey) (ADS)

Additional information related to the exposure of humans to the active substance contained in biocidal products.

Evaluation of residues in food and feed from biocidal uses requires information on the nature of residues as well as quantification of residues, which is covered by data requirements listed under this endpoint in Annex II of the BPR (and the endpoint 8.10 in Annex III of the BPR).

Dietary Risk Assessment (DRA) follows a step-wise approach with each step leading to a more realistic estimate of residue amounts in foods. Lower-level steps generally involve calculation models populated with default values in the first tier with the possibility of including additional data in higher tiers. With few exceptions, data from product- and use-specific residue studies with foods are only necessary if lower tiers fail to exclude a consumer risk. In addition, Maximum Residue Limits (MRLs) must be set when specified threshold amounts in foods are exceeded.

The basic use categories for DRA are "animal husbandry", "biocide-food contact (professional use)" and "biocide-food contact (non-professional use)". Depending on the use category, different calculation models and residue study designs apply. While some required information, e.g. metabolism in livestock and degradation during food processing is related to the active substance itself, other data are connected to the intended use of the respective biocidal product (e.g. supervised residue trials). The former can be submitted at the stage of the evaluation for active substance approval, while the latter must be generated at the product authorisation stage.

Guidance (under development) for dietary risk assessment should be followed.

8.16.1. Proposed acceptable residue levels i.e. maximum residue limits (MRL) and the justification of their acceptability (ADS)

For product-type 5, any relevant regulations relating to acceptable or unacceptable residues in drinking water must be taken into consideration in the justification.

For product-type 21, any directions or restrictions at the Community or national level related to residues in fish and shellfish intended to be used as food or feeding stuffs must be taken into consideration in the justification.

8.16.2. Behaviour of the residue of the active substance, its degradation products and, where relevant, its metabolites on the treated or contaminated food or feeding stuffs including the kinetics of disappearance (ADS)

Residue definitions should be provided where relevant. It is also important to compare residues found in toxicity studies with residues formed in food-producing animals, their product as well as food and feed.

8.16.3. Overall material balance for the active substance (ADS)

Sufficient residue data from supervised trials on food producing species and their products as well as food and feed to demonstrate that residues likely to arise from the proposed use would not be of concern for human or animal health

8.16.4. Estimation of potential or actual exposure of the active substance to humans through diet and other means (ADS)

Expected exposure via diet taking into account consideration the average consumption of different food types and drinking water should be studied.

8.16.5. If residues of the active substance remain on feeding stuffs for a significant period of time or also residues found in food of animal origin after treatment on or around food producing animals (ADS)

(E.g. direct treatment on animals or indirect treatment of animal houses or surroundings) then feeding and metabolism studies in livestock shall be required to permit evaluation of residues in food of animal origin

8.16.6. Effects of industrial processing and/or domestic preparation on the nature and magnitude of residues of the active substance

Provide information as implied by the title.

8.16.7. Any other available information that is relevant (ADS)

It may be appropriate to include information on migration into food, especially in the case of treatment of food contact materials

e.g. information from other chemical programmes on ADI, MRL or relevant residues

8.16.8. Summary and evaluation of data submitted under 8.16.1. to 8.16.7. (ADS)

It is important to establish whether the metabolites found in food (from animals or plants) are the same as those tested in toxicity studies. Otherwise values for risk assessment (e.g. ADI) are not valid for the residues found

Please follow the guidance in Chapter II Section 8.18.

8.17. If the active substance is to be used in products for action against plants including algae then tests to assess toxic effects of metabolites from treated plants, if any, where different from those identified in animals, shall be required (ADS)

This point on action against plants is considered as covered sufficiently by Regulation (EC) No 1107/2009 (PPPR).

8.18. Summary of mammalian toxicology

Provide overall evaluation and conclusion with regard to all toxicological data and any other information concerning the active substances including NOAEL.

9. Ecotoxicological studies

The ability of the active substance to damage the function and structure of ecosystems has to be clarified with a selection of ecotoxicity tests. All available biological data and information which is relevant to the assessment of the ecotoxicological profile of the active substance must be reported. The information provided must be sufficient to permit an assessment of the impact on non-target species likely to be exposed. The information provided must also be sufficient to permit hazard classification of the active substance (bioaccumulative, toxic) in accordance with CLP Regulation.

In the following, the words "active substance" or "substance" may also refer to metabolites, degradation or reaction products. It may be necessary to conduct separate studies for these when a potential impact cannot be sufficiently evaluated from the ecotoxicological profile of the active substance alone. Before such separate studies are performed, relevant information pertaining to metabolites, degradation or reaction products submitted in accordance with other relevant sections of Annex II to the BPR has to be taken into account. The information derived from the tests must permit a characterisation of the ecotoxicological significance of the metabolites, degradation or reaction products, and also reflect the nature and extent of the effects on non-target organisms and ecosystems.

Depending on the use and emission of the active substance, additional exposure-driven testing may be required. Tests should be performed with species representative of the environmental compartments and habitats that are exposed. Where relevant the mode of action of the substance should also be considered for selecting appropriate species. Further Guidance on exposure-driven information requirements is given in the product-type-specific guidance (Chapter V).

Testing on vertebrate animals must only be performed as a last resort, and only when the purpose and use of a product so requires. The applicant is also obliged to inquire from ECHA whether a certain vertebrate animal study is already available. Should this be the case, the test data must be shared (BPR Preamble 57 and Article 62). Absent or only low exposure to a substance may permit omitting a study if it is judged that further effect data would not help to make a better informed risk assessment. Accordingly, if a risk is found in a preliminary assessment, a refinement of the exposure assessment should be performed before further tests with vertebrate animals are carried out. Furthermore, alternative testing approaches, such as *in vitro* or *in silico* methods must be employed before a vertebrate animal test is carried out.

Further information on non-submission of data can be found in Chapter I Section 1.5. Further Guidance on alternative methods and limiting of live animal studies can be found amongst others in Annex IV of the BPR and a number of ECHA publications: (ECHA, 2008b); (ECHA, 2010b); (ECHA, 2011a) and (ECHA, 2012c).

Further Guidance providing more comprehensive background information to each data requirement and its use in the risk assessment can be found in the ECHA Guidance on information requirements, Chapter R.7b-c (ECHA, 2012c) respectively the TGD on risk assessment, Part II (EU, 2003). Other guidelines from e.g. US EPA or EFSA may also be useful for some data requirements and will be referenced specifically.

Aspects to consider for conducting and reporting ecotoxicological studies
Where relevant, tests should be designed and data analysed using appropriate statistical methods. Full details of the statistical analysis should be reported (e.g. all point estimates should be

provided with confidence intervals, exact probability values should be provided rather than stating significant/insignificant).

Preference should be given to test protocols and species for which existing guidelines or published studies are available.

9.1. Toxicity to Aquatic Organisms

Aspects to consider for testing on aquatic organisms
When carrying out ecotoxicity tests on aquatic organisms, it is required to measure the solubility and stability of the substance in the test medium, as it may differ from the results obtained in the water solubility test (Chapter II Section 3.9). In addition the Guidance for the environmental effects assessment for biocidal active substances that rapidly degrade in environmental compartments of concern (EU, 2009a) is relevant for testing rapidly degrading active substances. Concentrations up to 100 mg/L should be tested. A limit test at 100 mg/L may be performed when results of a range-finding test indicate that no effects are expected.

Additional tests with aquatic organisms may be needed to refine the initial risk assessment, as they may help to reduce the uncertainty. For this purpose, further short term testing on invertebrates or fish is not useful. Likewise, short term testing may not be necessary if long term studies are available.

Additional tests may also be required if there are uncertainties that require additional environmental effects information. For example, because of the environmental fate or the mode of action of the substance, or because of exposure to different environments or habitats.
If the data from the base set (algae, daphnids and fish) shows that one trophic level is more sensitive, and this is also corroborated by the mode of action of the substance, additional ecotoxicity studies that are required because of exposure to the marine or brackish environment may only need to be supplied for the most sensitive trophic level. To contribute to reduction of the uncertainty in the PNEC derivation any such additional studies should be long term.

For the purpose of PNEC derivation or refinement, interchangeable use of marine and freshwater ecotoxicity data is possible if the difference in sensitivity between freshwater and marine organisms belonging to the same trophic level is within a factor of 10. This would indicate that no specific environmental condition is more relevant for the effect assessment.

Differences in sensitivity can be judged for acute (EC_{50}; LC_{50}) as well as chronic (NOEC; LOEC; EC_{10}) endpoints. NOEC and LOEC values should however be used with caution as they are influenced by the dosing regime and the statistical power of the test.

In comparison to the PNEC setting for the freshwater environment, an additional assessment factor of 10 always applies for the marine (including brackish) environment, regardless of whether the data supplied is acute or chronic, or representative of marine or freshwater taxa. This additional uncertainty factor reflects the higher biodiversity in marine ecosystems compared to freshwater ecosystems, which may result in a broader distribution of species sensitivities. For brackish environments such as the Baltic Sea it represents an ecosystem with low biodiversity which is particularly sensitive to perturbations because of low ecological redundancy (TGD, (EU, 2003)). Only by conducting further studies with additional marine taxonomic groups, for example rotifers, echinoderms or molluscs, can the uncertainties with respect to the marine risk assessment be reduced and the additional assessment factor for the risk assessment be lowered. Further considerations in the TGD (EU, 2003) on the PNEC setting for the freshwater and marine environments apply.

Further Guidance for the selection of appropriate additional aquatic tests is given in the guidance for product-type-specific testing in Chapter V, as well as in the TGD (EU, 2003), respectively in ECHA Guidance on information requirements, Chapter R.7b-c (ECHA, 2012c).

9.1.1. Short term toxicity testing on fish

When short-term fish toxicity data is required the threshold approach (tiered strategy) should be applied

One species should be tested, preferably a fresh water species or, if different aquatic environments are exposed, two species may be required. The two species selected should represent freshwater and marine (or brackish) environments. *Cyprinodon variegatus* may be used as marine species in the OECD Test Guideline 203 (Fish, Acute Toxicity Test) or the US EPA guideline OPPTS 850.1075 (Fish Acute Toxicity Test, Freshwater and Marine).

The study does not need to be conducted if a valid long-term aquatic toxicity study on fish is available.

The threshold approach (tiered strategy) according to the OECD Guidance Document must be considered: essentially the approach uses a limit test at a single threshold concentration determined by the results of *Daphnia magna* and algae tests. If no mortality is observed in the limit test, the fish acute value can be expressed as greater than the threshold value. However, if mortality is observed a full concentration-response test is triggered. So for an active substance testing would occur with alga and *Daphnia magna*, the lower of the two concentrations would then be used in a limit test for fish. See the OECD Draft guidance 'The Threshold Approach for Acute Fish Toxicity Testing' for further details.

9.1.2. Short term toxicity testing on aquatic invertebrates

9.1.2.1. Daphnia magna

Test according to EC method C.2 (*Daphnia sp.* Acute Immobilisation Test) or the corresponding OECD Test Guideline 202 (*Daphnia sp.* Acute Immobilisation Test). Testing may be omitted if results are available from any non-standard test protocols, also with a different invertebrate species. The relevance of any such data as a surrogate should be decided in a weight of evidence approach.

9.1.2.2. Other species (ADS)

In addition to *D. magna,* a broad range of other aquatic invertebrates can be tested for acute toxicity. For example, additional marine or brackish data may be necessary for the risk assessment. Alternatives to OECD test guidelines are publications from ASTM International and ISO as well as the US EPA Office of Prevention, Pesticides and Toxic Substances (OPPTS). Various aquatic testing methods described in the scientific literature and elsewhere are consolidated and evaluated with respect to their feasibility for routine testing and standardisation in the OECD Series on testing and Assessment No. 11 Detailed Review Paper on Aquatic Testing Methods for Pesticides and Industrial Chemicals (OECD, 1998). The review includes testing methods for the pelagic environment for a range of insect species such as mosquitoes, caddisflies, stoneflies and mayflies.

Most of the references cited in Section 9 are exclusively for either freshwater or saltwater species. There are, however, some guidelines that are suitable for the testing of both freshwater and marine species.

9.1.3. Growth inhibition study on algae

9.1.3.1. Effects on growth rate on green algaeTest according to EC method C.3(Algae inhibition test) or the corresponding OECD guideline No. 201 (Freshwater Alga and Cyanobacteria, Growth Inhibition Test).

Test according to EC method C.3 (Algal inhibition test) or the corresponding OECD Test Guideline 201 (Freshwater Alga and Cyanobacteria, Growth Inhibition Test), or for a marine species a test according to, for instance the ISO 10253 (Water quality -- Marine algal growth inhibition test with Skeletonema costatum and Phaeodactylum tricornutum). For a marine or brackish water species e.g. the US-EPA guideline OPPTS 850.5400 (Algal toxicity, Tiers I and II) may be used.

9.1.3.2. Effects on growth rate of cyanobacteria or diatoms

Required for phytotoxic and/or antimicrobial substances. Should be studied with one species, preferably a fresh water species. Tests with additional marine or brackish species such as *Skeletonema costatum* (diatom) according to the ISO 10253 (Water quality - Marine algal growth inhibition test with Skeletonema costatum and Phaeodactylum tricornutum), or *Anabaena flos-aquae* (cyanobacterium representative of both fresh and brackish environments) for OECD Test Guideline 201 (Freshwater Alga and Cyanobacteria, Growth Inhibition Test) or the US EPA method OPPTS 850.5400 (Algal Toxicity, Tiers I and II) may be required if there is exposure.

9.1.4. Bioconcentration

This data requirement is closely related to the endpoint 9.1.7 – Bioaccumulation. The static bioconcentration factor (BCF) is the ratio of the internal concentration of a substance in an organism to the concentration in water (or other external medium) once a steady state has been achieved. Bioaccumulation refers to the net result of absorption (uptake) via different routes, distribution, metabolism and excretion of a substance in the organism.

An estimation of the intrinsic potential for bioconcentration in aquatic organisms should be submitted on the basis of physical and chemical properties (e.g. partition coefficient n-octanol/water). For surface active substances (surface tension lower than 60 mN/m) and dissociating or inorganic substances such as metals, toxicokinetic studies (including metabolism), residue studies or monitoring data on aquatic organisms (e.g. residue data in aquatic organisms and environmental concentrations) should be submitted.

Further Guidance:

- ECHA Guidance on information requirements Chapter R.7.10.1 Aquatic bioaccumulation (ECHA, 2012c)

9.1.4.1. Estimation methods

For estimation of BCF, see TGD (EU, 2003) Chapter 3.

The evaluation of aquatic bioconcentration should include an estimate of the bio-concentration factor related to absorption of the substance via the food chain.

9.1.4.2. Experimental determination

Test according to OECD Test Guideline 305 (Bioaccumulation in Fish: Aqueous and Dietary Exposure) or the EC method C.13 (Bioconcentration: Flow-through Fish Test).

The experimental determination may not need to be carried out if it can be demonstrated on the basis of physico-chemical properties (e.g. log K_{ow} <3) or other evidence that the substance has a low potential for bioconcentration. All critical aspects of bioaccumulation such as ionic speciation, surface activity and metabolic transformation rates must be considered before experimental determination is considered unnecessary.

9.1.5. Inhibition of microbial activity

Test according to EC method C.11 (Biodegradation: Activated Sludge Respiration Inhibition) or the corresponding OECD Test Guideline 209 (Activated Sludge, Respiration Inhibition Test).

The study may be replaced by a nitrification inhibition test if available data show that the substance is likely to be an inhibitor of microbial growth or function, in particular nitrifying bacteria.

All available data on the toxicity to micro-organisms in the sewage treatment plant should be reviewed and evaluated. Further testing should be evaluated according to the integrated testing strategy, in the ECHA Guidance on information requirements, R.7b (ECHA, 2012c).

9.1.6. Further Toxicity Studies on Aquatic Organisms (ADS)

If the results of the ecotoxicological studies, studies on fate and behaviour and/or the intended use(s) of the active substance indicate a risk for the aquatic environment, or if long-term exposure is expected, then one or more of the tests described in this Section shall be conducted. See also the product-type-specific guidance in Chapter V.

Further Guidance on the selection of long term aquatic toxicity tests on the basis of results from short term tests is given in TGD (EU, 2003) respectively (ECHA, 2012c) Chapter R.7.8.5.3 Conclusions on Chemical Safety Assessment (PNEC Derivation).

Further ecotoxicity testing would not normally be required on aquatic species for which no short term toxicity has been demonstrated (L(E)C_{50} >100 mg/l); exemptions may be substances poorly soluble in water. For these, long term testing might be required.

9.1.6.1. Long term toxicity testing on fish (ADS)

(a) Fish Early Life Stage (FELS) Test (ADS)

Test according to OECD Test Guideline 210 (Fish, Early-Life Stage Toxicity Test). It should be performed where long term fish toxicity data is required and the substance has the potential to bioaccumulate. For marine environments, the test can be performed with *Cyprinodon variegates*. The test is considered as the most sensitive of the fish tests, covering several life stages from the newly fertilised egg, through hatching to early stages of growth. This is believed to cover most, but not all, of the sensitive stages in the life-cycle. The FELS test is together with the full life cycle test the only suitable approach for examining the potential toxic effects of bioaccumulation.

(b) Fish short term toxicity test on embryo and sack fry stages (ADS)

Test according to EC method C.15 (Fish, short-term toxicity test on *embryo* and *sac-fry* stages) or the corresponding OECD Test Guideline 212 (Fish, Short-term Toxicity Test on Embryo and Sac-Fry Stages). It is considered as an alternative to the FELS test for substances with log Kow < 4. For marine environments, the guideline proposes several species, e.g. *Cyprinodon variegatus*. The test covers the sensitive early life stages from the newly fertilised egg to the end of the sac-fry

stage. It is considerably shorter, and hence cheaper, than the FELS test but is also considered to be less sensitive.

(c) Fish juvenile growth test (ADS)

Test according to EC method C.14 (Fish Juvenile Growth Test) or the corresponding OECD Test Guideline 215 (Fish, Juvenile Growth Test). The test provides a shorter and cheaper option to the FELS test for substances with log Kow < 5. Although it is considered to be of insufficient duration to examine all the sensitive stages in the fish life cycle, it covers the growth of juvenile fish over a fixed period and is as such considered as a sensitive indicator of fish toxicity.

(d) Fish full life cycle test (FFLCT) (ADS)

Such a test may be necessary if results from other long-term studies with fish indicate concern (see also Chapter II Section 9.10. - Identification of endocrine activity).

There are currently no agreed guidelines available for a FFLCT, although two reviews of existing testing approaches and protocols under development are available, the OECD Series on Testing and Assessment No. 95 Detailed Review Paper on Fish Life-cycle tests (OECD, 2008c) and No. 171 Fish Toxicity Testing Framework (OECD, 2012a), including the Japanese medaka multi-generation test as well as one-generation FFLCT likely to be sufficient to satisfy regulatory requirements.

Although FFLCTs are generally more sensitive to endocrine disruptors than partial life cycle reproduction tests, it has not yet been demonstrated that two-generation or multi-generation tests with fish offer any further advance in sensitivity (OECD, 2012a). Nevertheless, a two-generation or multi-generation FFLCT is likely to provide an optimal response to all possible modes of chemical toxicity (endocrine and non-endocrine), and as such could be considered as providing a 'gold standard' result on developmental and reproductive endpoints. Such a test would provide definitive data on the long term fish toxicity of a substance, although these are not necessarily indicative or specific to any particular mode of action.

9.1.6.2. Long term toxicity testing on invertebrates (ADS)

a) Daphnia growth and reproduction study (ADS)
The relevant test is OECD Test Guideline 211 (D*aphnia magna* Reproduction Test).

b) Other species reproduction and growth (e.g. Mysid) (ADS)
Tests with an aquatic insect should be performed first for insecticidal substances or substances considered to interfere with insect moulting hormones or that have other effects on insect growth and development. Tests involving sensitive life stages, special routes of uptake or other modifications, may be necessary. The rationale for the choice of test species and exposure conditions used should be provided. For the marine environment, the shrimp *Mysidopsis bahia* is the preferred test species and the relevant test is the US EPA guideline OPPTS 850.1350 (Mysid Chronic Toxicity Test). For relevant freshwater species, see Chapter II Section 9.1.6.2(c).

Test methods for other marine species and organism groups are available, e.g.:

- Polychaetous Annelids: ASTM E1562 'Standard Guide for Conducting Acute, Chronic, and Life-Cycle Aquatic Toxicity Tests with Polychaetous Annelids'.
- *Nitocra spinipes* (copepod, marine): Danish standard DS 2209:1990 (Water quality - Acute ecotoxicological test with the crustacean *Nitocra Spinipes* - Static method).

Aquatic testing methods for a variety of taxonomic groups such as marine and/or freshwater amphipods, bivalves, crustaceans and echinoderms described in the scientific literature and

elsewhere are consolidated in the OECD Series on testing and Assessment No. 11 (Detailed Review Paper on Aquatic Testing Methods for Pesticides and Industrial Chemicals). The species tested should be representative of the exposed environment.

c) Other species development and emergence (e.g. Chironomus) (ADS)
Tests with an aquatic insect should be performed first for insecticidal substances or substances considered to interfere with insect moulting hormones or that have other effects on insect growth and development. Tests involving sensitive life stages, special routes of uptake or other modifications, may be necessary. The rationale for the choice of test species and exposure conditions used should be provided.

The relevant test for Chironomus sp. is OECD Test Guideline 219 (Sediment-Water Chironomid Toxicity Using Spiked Water). If the substance is likely to accumulate in the sediment, the OECD Test Guideline 218 *Chironomus sp.* method for spiked sediment should be used instead to reflect the major route of exposure (see Chapter II Section 9.1.9. - Studies on sediment dwelling organisms).

Another relevant insect species is *Chaoborus sp*. (with several species such as *Chaoborus obscuripes*, *Chaoborus flavicans*, *Chaoborus crystallinus* and *Chaoborus americanus*). Chronic test methods with mayflies (*Cloeon sp.*, *Stenonema sp.* and *Epeorus sp.*) for the freshwater pelagic environment are described in the scientific literature and may be considered if motivated by exposure route. These tests have been given relatively high overall evaluation scores (with respect to their feasability for routine testing) in an OECD review paper on aquatic testing methods (OECD Series on testing and Assessment No. 11, Detailed Review Paper on Aquatic Testing Methods for Pesticides and Industrial Chemicals (OECD, 1998).

9.1.7. Bioaccumulation in an appropriate aquatic species (ADS)

Bioaccumulation studies should be conducted when the substance has surface activity (i.e. surface tension < 60 mN/m at a concentration $\leq$ 1 g/l) or structural features indicating bioaccumulation (as in the case of e.g. pyridinium compounds).

There may also be other grounds for testing. A test with fish is required when there is the risk for secondary poisoning. For marine environments, *Cyprinodon variegatus* should be tested according to the EC method C.13 (Bioconcentration: Flow-Through Fish Test) or preferably the corresponding OECD Test Guidelines 305 (Bioaccumulation in Fish: Aqueous and Dietary Exposure). A range of other fish species may also be tested with this method. Testing during a juvenile life stage with rapid growth should be avoided as growth dilution might then extensively influence the outcome. In any case, the fish must be weighed to correct the results for this factor (OECD, 2012a).

Studies with invertebrates may be required for some product-types, especially if a direct release to marine or brackish environments occurs (see also the product-type-specific guidance in Chapter V). Test protocols suitable for several species are available:

- *Mytilus edulis* (mussel, marine); Pecten spp. (scallop, marine); *Crassostrea gigas* or *C. virginica* (oyster, marine) ASTM E1022 (Standard Guide for Conducting Bioconcentration Tests with Fishes and Saltwater Bivalve Mollusks).
- Nereis virens or Capetella sp. (polychaetes, marine), Macoma balthica, M. nasuta or Yoldia imatula (clams, marine); Diporeia sp. (amphipod, freshwater); Chironomus tentans (midge, freshwater); Hexagenia sp. (mayfly, freshwater) ASTM E1688 (Standard Guide for Determination of the Bioaccumulation of Sediment-Associated Contaminants by Benthic Invertebrates).

- *Crassostrea virginica* (oyster, marine): US-EPA OPPTS 850.1710 (Oyster BCF)

9.1.8. Effects on any other specific, non-target organisms (flora and fauna) believed to be at risk (ADS)

Data may be required for non-target organisms other than fish, microalgae and invertebrates if concerns are raised from the uses and emissions of the active substance, effects detected on other aquatic species, or a preliminary risk assessment. This may involve tests on sediment dwelling organisms and aquatic macrophytes, accumulation and elimination in shellfish, or tests with additional brackish or marine organisms.

9.1.9. Studies on sediment dwelling organisms (ADS)

When accumulation of an active substance in an aquatic sediment is indicated or predicted by environmental fate studies, the impact on a sediment-dwelling organism should be assessed. Testing might be required for certain product-types (see product-type-specific Guidance in Chapter V) or if the risk assessment for sediment based on the equilibrium partition method indicates a possible risk to the benthic compartment.

The selection of test species should be made on the basis of mode of action information coupled to biological traits, as representatives of different taxonomic groups are available, but also habitat and feeding strategy to reflect different routes of exposure among sediment organisms. In this context, a distinction could be made between epibenthic deposit feeders (Chironomids) and endobenthic sediment ingesters (Oligochaetes). To make a distinction between sediments of different composition rather than different species, it is also recognised that the variability of sediment could be as relevant for the outcome of the test as species sensitivity. Normalisation to default organic matter is not foreseen in the TGD (EU, 2003) for sediment studies. However, it should be clearly indicated whether the organic matter content is in line with the Guidance, or strongly deviates from it, since this may influence the quality of the study.

Organisms should be exposed to spiked sediment. The presence of spiked sediment is essential because the substances for which testing is required are typically very hydrophobic substances or substances that bind covalently to sediment. Long-term tests should be performed and one long-term NOEC or EC_{10} value should be sufficient at the first stage. This value will be based on the measured bulk sediment concentration. If further refinement of the PNEC would be necessary, test species with different habitats and feeding strategies should be preferred to reflect the possible different ways of exposure.

The following recommendations can be made with respect to the test species. The recommended species are complementary to each other with respect to feeding strategy and habitat:

- Long-term Chironomid toxicity test (spiked sediment). Test according to OECD Test Guideline 218 (Sediment-Water Chironomid Toxicity Using Spiked Sediment). This test should be considered first for insecticidal substances or substances considered to interfere with insect moulting hormones or that have other effects on insect growth and development.

- Long-term Oligochaete test (spiked sediment). If testing is needed, preference should be given to an endobenthic sediment ingester to reflect different habitat and feeding strategies. Oligochaetes such as *Tubifex sp.* or *Lumbriculus sp.* would be suitable candidates. Standardised tests for these species are OECD Test Guideline 225 (Sediment-Water Lumbriculus Toxicity Test Using Spiked Sediment) the ASTM E1367 (Standard Test Method for Measuring the Toxicity of Sediment-Associated Contaminants with Estuarine

and Marine Invertebrates) and the ASTM E1706 – (Standard Test Method for Measuring the Toxicity of Sediment-Associated Contaminants with Freshwater Invertebrates).

- Long-term test (spiked sediment) with *Gammarus sp.* or *Hyalella sp.* This could be considered if a test with a third species would be necessary to reduce the uncertainty in the effect assessment. Alternatively, testing with a second sediment sample could be considered. *Gammarus sp.* and *Hyalella sp.* are epibenthic deposit feeders, but the difference with *Chironomus sp.* is apart from belonging to different taxonomic groups that they spend their whole life cycle on the sediment. Standardised tests are described in the ASTM E1367 and E1706.

9.1.10. Effects on aquatic macrophytes (ADS)

A test with *Lemna* sp. according to OECD Test Guideline 221 (*Lemna sp.* Growth Inhibition Test) should be performed for herbicides, plant growth regulators, and fungicides, where there is evidence that the test compound has herbicidal activity. The test should provide information on inhibition of growth and yield based on frond numbers, and on a second variable such as frond area, dry weight, or fresh weight.

If the test compound is an auxin inhibitor, or if there are clear indications from efficacy data or from testing with terrestrial non-target plants for higher toxicity to dicotyledonous plant species, then a test should be carried out using a dicotyledon species. A test protocol specifically for *Myriophyllum sibiricum* was available ASTM E1913 (Standard Guide for Conducting Static, Axenic, 14-Day Phytotoxicity Tests in Test Tubes with the Submersed Aquatic Macrophyte, *Myriophyllum sibiricum* Komarov) but was withdrawn in 2012 without replacement. More general guidelines for a variety of freshwater emergent macrophytes are available in ASTM E1841 (Standard Guide for Conducting Renewal Phytotoxicity Tests With Freshwater Emergent Macrophytes). The tests should provide sufficient information to evaluate impact on aquatic plants and include details of the inhibition of shoot length, inhibition of root number and length and inhibition of fresh or dry weight.

9.2. Terrestrial toxicity, initial tests (ADS)

These tests are required if the risk assessment for the terrestrial compartment, based on the equilibrium partitioning method indicates a concern for the terrestrial compartment, or if there is direct or long term exposure. If there is potential continuous exposure, long-term test (see Chapter II Section 9.3) should be considered instead. For some product-types, these tests will be required with the core data set (see the product-type-specific guidance in Chapter V for further details). It is necessary to submit ecotoxicity data on all three points 9.2.1 - 9.2.3 to allow a derivation of a more realistic PNEC for the terrestrial compartment than the PNEC based on the equilibrium partitioning method.

All effect concentrations from earthworms, terrestrial plants and terrestrial micro-organisms should be converted to the TGD standard soil organic matter content (3.4%) before choosing one effect value for derivation of the PNEC (EU, 2003). As stated in the TGD this is only appropriate when it can be assumed that the binding behaviour of a non-ionic organic substance in question is predominantly driven by its log K_{ow} and that organisms are exposed predominantly via pore water.

9.2.1. Effects on soil micro-organisms (ADS)

One or more of the following tests should be conducted:

- A test on effects on nitrogen transformation and/or carbon mineralisation in soil according to the EC method C.21 (Soil Micro-organisms: Nitrogen Transformation Test) or the corresponding OECD Test Guideline 216 (Soil Micro-Organisms, Nitrogen Transformation Test), or the EC method C.22 (Soil Micro-organisms: Carbon Transformation Test) or the corresponding OECD Test Guideline 217 (Soil Micro-Organisms, Carbon Transformation Test), respectively.
- A test on inhibition of soil non-target micro-organisms according to the ISO 14238:2012 (Soil quality - Biological methods - Determination of nitrogen mineralisation and nitrification in soils and the influence of chemicals on these processes), or the BBA guideline Part VI, 1.1 (Effects on the activity of the soil microflora), or the DIN EN ISO 23753-2 (Soil quality - Determination of dehydrogenase activity in soils - Part 2: Method using iodotetrazolium chloride).

9.2.2. Effects on earthworms or other soil-dwelling non-target invertebrates (ADS)

One or more of the following tests should be conducted:

- *Lumbricina* (earthworm): Test according to EC method C.8 (Toxicity to Earthworms) or the corresponding OECD Test Guideline 207 (Earthworm, Acute Toxicity Tests).
- *Caenorhabditis elegans* (nematode) according to the ASTM method E2172 (Standard Guide for Conducting Laboratory Soil Toxicity Tests with the Nematode *Caenorhabditis elegans*)

For insecticidal substances an arthropod is the preferred test species for assessing survival under short-term acute exposure. For example, *Aleochara bilineata* (rove beetle), *Poecilus cupreus* (carabid beetle), or *Pardosa sp.* (wolf spider) according to the IOBC 'Guidelines to evaluate side-effects of plant protection products to non-target arthropods' (IOBC, 2000). Tests involving sensitive life stages, special routes of uptake or other modifications, may be necessary. The rationale for the choice of test species and exposure conditions used should be provided.

9.2.3. Acute toxicity to plants (ADS)

Test according to OECD Test Guideline 208 (Terrestrial Plant Test: Seedling Emergence and Seedling Growth Test), or OECD Test Guideline 227 (Terrestrial Plant Test: Vegetative Vigour Test). Where it can be clearly demonstrated by the mode of action that either seedling emergence or vegetative vigour is affected, only the relevant test should be conducted. The exposure pathway should also govern which test to conduct. For active substances emitted to the environment through spray drift, additionally a test with plant surface treatment should be performed.

Data on species from different taxa of monocotyledons and dicotyledons must be provided, including at least one nitrogen fixating species (*e.g.,* Leguminosae). At least three species must have been tested according to these OECD Test Guidelines.

9.3. Terrestrial tests, long term (ADS)

These tests are required if the risk assessment for the terrestrial compartment based on the results from the acute toxicity tests indicates a concern, or if there is potential continuous exposure. For the risk assessment, the NOEC from the test on inhibition of soil micro-organisms

(Chapter II Section 9.2.1) can be used as long-term result. The NOEC from the acute plant study (Chapter II Section 9.2.3) can also be used as a long-term result if, on the basis of the acute tests earthworms and micro-organisms are more sensitive. A chronic test for plants (ISO 22030 'Soil quality - Biological methods - Chronic toxicity in higher plants') is required if the acute tests show that plants are the most sensitive group.

Further Guidance:

- TGD (EU, 2003),
- ECHA Guidance on information requirements and chemical safety assessment Chapter R.7.11.5.3 Concluding on suitability for use in Chemical Safety Assessment (ECHA, 2012c)

9.3.1. Reproduction study with earthworms or other soil-dwelling non-target invertebrates (ADS)

One or more of the following tests should be conducted:

- *Lumbricina* (earthworm) according to OECD Test Guideline 222 (Earthworm Reproduction Test (*Eisenia fetida*/*Eisenia andrei*)), alternatively the ISO 11268-1 (Soil quality - Effects of pollutants on earthworms - Part 1: Determination of acute toxicity *to Eisenia fetida*/*Eisenia andrei*)
- *Enchytraeid* (enchytraeid worm), according to OECD Test Guideline 220 (Enchytraeid Reproduction Test) alternatively the ISO 16387 (Soil quality - Effects of pollutants on Enchytraeidae (*Enchytraeus sp.*) - Determination of effects on reproduction and survival)

For insecticidal substances or substances considered to interfere with insect moulting hormones or that have other effects on insect growth and development, an arthropod is the preferred test species. *Hypoaspis (Geolaelaps) aculeifer* (predatory mite) according to OECD Test Guideline 226 (Predatory mite (*Hypoaspis (Geolaelaps) aculeifer*) reproduction test in soil; *Folsomia candida* (springtail) according to OECD Test Guideline 232 (Collembolan Reproduction Test in Soil) alternatively the ISO 11267 (Soil quality - Inhibition of reproduction of Collembola (*Folsomia candida*) by soil pollutants), *Aleochara bilineata* (rove beetle), *Poecilus cupreus* (ground beetle), or *Pardosa sp.* (wolf spider) according to the IOBC (IOBC, 2000). Tests involving sensitive life stages, special routes of uptake or other modifications, may be necessary. The rationale for the choice of test species and exposure conditions used should be provided.

9.4. Effects on birds (ADS)

For some product-types, where direct exposure for birds is possible tests with birds are required. This is also the case where a first risk assessment for birds, e.g. on the conclusions of mammalian toxicity data or bioaccumulation data indicates concern.

However, the bird tests are associated with high animal welfare concerns and there is a risk that results will only be of limited regulatory and scientific use. This is especially of concern for the acute oral toxicity study as indicated in Chapter II Section 9.4.1. below.

Further Guidance:

- ECHA Guidance on information requirements and chemical safety assessment (ECHA, 2012c);
- EFSA Guidance Document on Risk Assessment for Birds and Mammals. (EFSA, 2009a)

9.4.1. Acute oral toxicity (ADS)

Test according to OECD Test Guideline 223 (Avian Acute Oral Toxicity Test) or SETAC Procedures for Assessing the Environmental Fate and Ecotoxicity of Pesticides (SETAC, 1995). The highest dose used in tests need not exceed 2000 mg/kg body weight. The acute oral toxicity study is of only limited use for PNEC derivation. Accordingly, this study should only be performed as a last resort and be chosen with care taking into account, e.g. exposure regime, environmental fate, and mode of action of the substance, as well the relevance of the particular study for the risk assessment. Alternative non-testing approaches must be exhausted, and where relevant a food avoidance study (OECD Draft Guidance document on avoidance testing of birds, (OECD, 2011)) should be performed first to investigate whether direct oral exposure, such as ingestion of pellets, is plausible.

9.4.2. Short-term toxicity – eight-day dietary study in at least one species (other than chickens, ducks and geese) (ADS)

Test according to OECD Test Guideline 205 (Avian Dietary Toxicity Test). If the test for effects on reproduction (Chapter II Section 9.4.3) is available, this test is not necessary.

The short term dietary study is criticised (EFSA, 2009b) for being associated with substantial methodological limitations that can hamper interpretation. On the basis of recommendations from the PPR Panel (EFSA, 2009b) the short term dietary study should be conducted only for substances where the mode of action and/or results from mammalian studies indicate a potential for the dietary LD_{50} measured by the short term study to be lower than the LD_{50} based on an acute oral study. This would apply, for instance, to many of the organochlorine compounds and anticoagulants like flocoumafen. The short-term dietary test should not be conducted for any other purpose unless it can be clearly justified. When the study is justified, it should be conducted with one species only. The short-term dietary test should not be used simply to demonstrate the potential for food avoidance, as this can be achieved satisfactorily with fewer birds in a shorter (one day) study.

9.4.3. Effects on reproduction (ADS)

Test according to OECD Test Guideline 206 (Avian Reproduction Test).

The study does not need to be conducted if the dietary toxicity study shows that the LC_{50} is above 2 000 mg/kg food.

9.5. Effects on arthropods (ADS)

A test on bees and/or other beneficial arthropods may be required for insecticides, acaricides and substances in products to control other arthropods which are used outdoors, i.e. for large scale-outdoor applications like fogging (e.g. product-type 18 - products against mosquitoes for human health reasons). Additionally, for systemic insecticides exposure to bees should also be quantified. When no data is available, a qualitative assessment should be performed.

Effects on arthropods do not usually have to be assessed for uses with indoor applications only. Tests may be needed in case of drift occurring from e.g. large cooling water systems or outdoor spray uses.

9.5.1. Effects on honeybees (ADS)

Tests on acute oral and/or contact toxicity on bees should be done according to OECD Test Guideline 213 (Honeybees, Acute Oral Toxicity Test) and respectively OECD Test Guideline 214

(Honeybees, Acute Contact Toxicity Test). Guidelines are also available for trials for side-effects on bees as the EPPO PP 1/170/(3) (Side-Effects on Honeybees), and for brood test under semi-field conditions the OECD Series on Testing and Assessment No. 75 (Guidance Document on the Honey Bee (*Apis Mellifera L.*) Brood Test Under Semi-Field Conditions).

9.5.2. Other non-target terrestrial arthropods, e.g. predators (ADS)

Possible species to be tested in addition to honeybees are for instance, *Chrysoperla carnea* (common green lacewing), *Trichogramma cacoeciae* (Hymenoptera egg parasitoid), *Coccinella septempuna* (ladybird) or *Aleochara bilineata* (rove beetle) according to the IOBC 'Guidelines to evaluate side-effects of plant protection products to non-target arthropods' (IOBC, 2000). Tests involving sensitive life stages, special routes of uptake or other modifications may be necessary. The rationale for the choice of test species and exposure conditions used should be provided.

9.6. Bioconcentration, terrestrial (ADS)

When released into soil the intrinsic bioconcentration potential needs to be estimated based on, at least, the physical-chemical properties of the substance (e.g. the partitioning coefficient, surface-active substances and dissociating or inorganic substances).

Further Guidance:

- TGD (EU, 2003); ECHA Guidance on information requirements and chemical safety assessment Chapter R.7.10.8 Terrestrial Bioaccumulation (ECHA, 2012c)

9.7. Bioaccumulation, terrestrial (ADS)

Bioaccumulation results from both bioconcentration and biomagnification, and is thus closely related to the assessment of bioconcentration.

For screening or first tier approaches, relevant computational methods (e.g. s or read-across) can be used to estimate the terrestrial bioaccumulation potential of a substance, if it is sufficiently justified and acceptable in each case.

Experimental studies on terrestrial bioaccumulation could be warranted if information from non-testing methods and/or bioconcentration studies indicate concern. Recommended test protocols for bioaccumulation in terrestrial oligochaetes are OECD Test Guideline 317 (Bioaccumulation in Terrestrial Oligochaetes) and ASTM E1676 (Standard Guide for Conducting Laboratory Soil Toxicity or Bioaccumulation Tests with the Lumbricid Earthworm *Eisenia Fetida* and the Enchytraeid Potworm *Enchytraeus albidus*). Results of bioaccumulation tests with suitable sediment-dwelling invertebrates (Chapter II Section 9.1.7) may provide useful comparative information that can be used in a weight of evidence approach. The recommended test protocol for bioaccumulation is the US EPA OPPTS 850.4800 (Plant Uptake and Translocation Test).

Further Guidance:

- TGD (EU, 2003);
- ECHA Guidance on information requirements and chemical safety assessment Chapter R.7c: R.7.10.8 Terrestrial Bioaccumulation (ECHA, 2012c)

9.8. Effects on other non-target, non aquatic organisms (ADS)

Further tests (e.g. field tests) may be required if the risk assessment based on long term terrestrial tests indicates that there is still a concern for the terrestrial compartment.

9.9. Effects on mammals (ADS)

Data are derived from the mammalian toxicological assessment. *The most sensitive relevant mammalian long-term toxicological endpoint (*NOAEL*) expressed as mg test compound/kg bw/day shall be reported.*

Additionally, the NOEC expressed as mg test compound /kg food should be reported. Please follow the Guidance in Chapter II Section 8.

9.9.1. Acute oral toxicity (ADS)

Please follow the Guidance in Chapter II Section 8.

9.9.2. Short term toxicity (ADS)

Please follow the Guidance in Chapter II Section 8.

9.9.3. Long term toxicity (ADS)

Please follow the Guidance in Chapter II Section 8.

9.9.4. Effects on reproduction (ADS)

Please follow the Guidance in Chapter II Section 8.

9.10. Identification of endocrine activity (ADS)

Commission's delegated acts specifying scientific criteria for determining endocrine-disrupting properties will be available from December 2013. Pending the adoption of these criteria, Article 5(3) of the BPR provides the following interim criteria:

- *Active substances that are classified in accordance with Regulation (EC) No 1272/2008 as, or meet the criteria to be classified as, carcinogen category 2 and toxic for reproduction category 2, shall be considered as having endocrine-disrupting properties (note that active substances classified as carcinogen category 1 and toxic for reproduction category 1 are considered as meeting the exclusion criteria).*
- *Substances such as those that are classified in accordance with Regulation (EC) No 1272/2008 as, or that meet the criteria to be classified as, toxic for reproduction category 2 a and that have toxic effects on the endocrine organs, may be considered as having endocrine-disrupting properties.*

Furthermore, Article 5(1)(d) states that active substances can be *identified in accordance with Articles 57(f) and 59(1) of Regulation (EC) No 1907/2006 as having* endocrine-disrupting properties (scientific evidence of probable serious effects to human health or the environment). Data on the toxicity profile and mode of action should be scrutinised as well as any other additional information. Moreover, there should be a consideration of all the existing data and Guidance as described in the OECD 'Guidance Document on the Assessment of Chemicals for Endocrine Disruption' (OECD, 2010).

If as a result of this initial consideration, the substance is identified as a potential endocrine disruptor, then agreement of the competent authorities on the need to perform additional studies and on the types of study to be performed should be sought. Fish testing should consider the need to conduct either OECD Test Guideline 229 (Fish Short Term Reproduction Assay) or OECD Test

Guideline 230 (21-day Fish Assay *A Short Term Screening for Oestrogenic and Androgenic Activity, and Aromatase Inhibition*). In the specific case that the endocrine disrupting effect is known to be based on aromatase inhibition (e.g. in certain ergosterolsynthesis-inhibiting fungicides) a fish sexual development test may be preferable (OECD Test Guideline 234 (Fish Sexual Development Test)). If the results indicate endocrine mediated effects, a full fish life cycle study should be considered (see Chapter II Section 9.1.6.1). Similarly, the need for amphibian testing should be considered (NB. such testing if conducted may also have relevance, possibly in terms of no mortality dose, for the overall assessment of risk to amphibians). Until the agreed Guidance is available, agreement of the competent authority on the specific tests required should be sought.

10. Environmental fate and behaviour

Information related to the fate and behaviour of the active substance and its degradation products in the environment is needed in order to be able to assess the exposure to the environment, for example, by the approximate estimation of the likely concentrations of the substance in the different compartments of the environment. The information is also relevant for the PBT assessment (P criterion) and for classification (CLP).

The data and information provided should be sufficient to:

- identify the relative importance of the types of processes involved (balance between chemical and biological degradation),
- where possible, identify the individual components present,
- establish the relative proportions of the components present and their distribution between water, including suspended particles, and sediment, and
- permit to define/determine the residue of concern and which non-target species are or may be exposed to it.

Product-type-specific Guidance on exposure-driven information requirements is given in Chapter V.
Fate and ecotoxicological studies are required for major metabolites and those ecotoxicologically relevant metabolites which give reason for concern. A risk assessment should be performed. Please refer to Chapter I Section 1.6 for a respective classification of metabolites.

Where radio-labelled test material is used, radio-labels should be positioned at sites (one or more as necessary) to facilitate the elucidation of metabolic and degradation pathways and to facilitate investigation of the distribution of the active substance and of its metabolites, reaction and degradation products in the environment.

10.1. Fate and behaviour in water and sediment

10.1.1. Degradation, initial studies

If the assessment performed indicates the need to investigate further the degradation of the substance and its degradation products or the active substance has an overall low or absent abiotic degradation, then the tests described in 10.1.3 and 10.3.2 and where appropriate - in 10.4 shall be required. The choice of the appropriate test(s) depends on the results of the initial assessment performed.

Further information is given in Chapter IV Testing Strategies.

10.1.1.1. Abiotic

(a) Hydrolysis as a function of pH and identification of breakdown products

The identification of breakdown products is required when the breakdown products at any sampling time are present at ≥10% of the added parent compound.

Hydrolysis must be examined at, at least, three different pH-values. A suggested temperature range is 10-70 °C (preferably with at least one temperature below 25 °C utilised), which will encompass the reporting temperature of 25 °C and most of the temperatures encountered in the field. For substances with a low hydrolysis rate, only the preliminary test carried out at 50 °C for five days may be sufficient. A substance of which less than 10% hydrolyses in five days at 50 °C (i.e. it is considered hydrolytically stable) needs no further testing for hydrolysis.

Test according to EC method C.7 (Degradation — Abiotic Degradation: Hydrolysis as a Function of pH) or the corresponding OECD Test Guideline 111 (Hydrolysis as a Function of pH).

(b) Phototransformation in water, including identification of transformation products

The data must be submitted for a purified active substance of stated specification.

The results submitted should correspond to the light intensities and spectral distribution from northern to southern European regions, for example, in 40 and 65 degrees (proposed average 50 degrees) northern latitude during spring and autumn. This may be presented e.g. by extrapolation.

In order to assess the contribution of photochemical degradation processes in water to the fate of the active substance, both direct and indirect aqueous photolysis needs to be considered (see TGD (EU, 2003), Part II, Chapter 2 Section 2.3.6.2). A consideration of the rate of indirect aqueous photolysis should only be included in cases where the rates of other aqueous degradation processes (hydrolysis, biodegradation, direct photolysis) are slow.

Test according to OECD Test Guideline 316 (Phototransformation of Chemicals in Water – Direct Photolysis), SETAC procedures (SETAC, 1995) or US-EPA guideline OPPTS 835.2210. For indirect photolysis, no harmonised testing guideline is currently available. QSARs to estimate the indirect photolysis rate may be relevant.

10.1.1.2. Biotic

In the following, initial biodegradation studies (core data) are described. However, it is possible to directly perform simulation studies for the relevant environmental compartments and skip initial biodegradation studies e.g. for those biocides which are toxic to the inoculum (more details on the testing strategy are provided in Chapter IV).

(a) Ready biodegradability

At least a screening test on ready biodegradation is always required for organic compounds, unless a simulation test for all environmental compartments considered relevant is available. Test according to any of the EC methods C.4 (Determination of 'Ready' Biodegradability) A-F or the corresponding OECD Test Guideline 301 (Ready Biodegradability) A-F taking especially notice of the Annex to these methods concerning the evaluation of the biodegradability of chemicals suspected to be toxic to the inoculum.

(b) Inherent biodegradability (where appropriate)

May be provided if available (if the compound is not readily degradable unless a simulation test for all relevant environmental compartments is provided). Simulation tests are preferred instead of new tests on inherent biodegradability. The testing strategy to follow is described in Chapter IV.

Test according to the EC method C.9 (Biodegradation — Zahn-Wellens Test) or the corresponding OECD Test Guidelines 302 B (Inherent Biodegradability: Zahn-Wellens/ EVPA Test) or according to 302 C (Inherent Biodegradability: Modified MITI Test (II)).

10.1.2. Adsorption/desorption

A screening test on adsorption/desorption is always required according to tier 2 of EC method C.18 (Adsorption/Desorption Using a Batch Equilibrium Method) or the corresponding OECD Test

Guideline 106 (Adsorption-Desorption Using a Batch Equilibrium Method). The adsorption is studied in five different soil types for the active substance and three different soil types for major metabolites by means of adsorption kinetics at a single concentration and determination of distribution coefficients K_d and K_{OC}. Although not explicitly mentioned in the guideline the handling procedure can also be applied to sediments.

An alternative method is the estimation of adsorption with HPLC, EC method C.19 (Estimation of the Adsorption Coefficient (K_{OC}) on Soil and on Sewage Sludge Using High Performance Liquid Chromatography (HPLC)) or the corresponding OECD Test Guideline 121 (Estimation of the Adsorption Coefficient on Soil and on Sewage Sludge Using HPLC). This method provides an estimate of a chemical's partitioning behaviour between aqueous phases and organic surfaces of soils, sediments and sludge (K_{OC}). This estimate is normally sufficient for a preliminary exposure assessment of substances. It should be noted however, that for some substances the HPLC-technique is not yet fully validated or applicable.

The testing strategy in Chapter IV indicates when further tests (according to Chapter II Sections 10.1.4., 10.2.4. or 10.2.5) would be necessary.

If a higher tier study is provided for one of the other endpoints for the relevant compartment(s), this endpoint might be waived.

10.1.3. Rate and route of degradation including identification of metabolites and degradation products (ADS)

10.1.3.1. Biological sewage treatment (ADS)

(a) Aerobic biodegradation (ADS)
Please refer to 10.1.3.1 (c) STP simulation test below.

(b) Anaerobic biodegradation (ADS)
An anaerobic degradation study may be required if exposure to anaerobic conditions is likely.

Test according to OECD Test Guideline 311 (Anaerobic Biodegradability of Organic Compounds in Digested Sludge: by Measurement of Gas Production) or ISO method 11734.

(c) STP simulation test (ADS)
The only laboratory STP simulation test currently available is the EC method C.10 (Biodegradation — Activated Sludge Simulation Tests) or the corresponding OECD Test Guideline 303 A (Simulation Test - Aerobic Sewage Treatment - A: Activated Sludge Units). In its original version, this test cannot distinguish between biological degradation and other elimination processes such as adsorption and volatilisation. In the last years several modifications of the 'activated sludge units' test were developed. As a result, it is at least possible to determine the amount of active substance and metabolites in water and sludge in test systems according to the mentioned test guidelines and to calculate a limited mass balance (without volatilisation). Test designs using closed systems with radiolabelled substances to get a complete mass-balance are approved as well. Even if the modified tests are not standardised internationally, the results may be used for the refinement of the exposure assessment.

If a STP simulation test according to EC method C.10 or OECD Test Guideline 303 A is performed today, it should generally satisfy the following requirements:

- Specific analyses of active substance and metabolites in effluent and sludge to calculate a limited mass balance.
- If possible the use of closed systems and radiolabelled substances to get a mass balance.

In recent years relatively simple tests using radio-labelled material have been developed which may provide useful information on e.g. aerobic degradation in an STP. They allow for the use of low substance concentrations, give primary degradation rates, account for formation (and disappearance) of metabolites, and are relatively easy to perform. Anyhow, at present here is no harmonised way to evaluate these tests; therefore the evaluating MSCA must be contacted before conducting such tests.

10.1.3.2. Biodegradation in freshwater (ADS)

This information is relevant for substances or transformation products that are released directly or indirectly to water/sediment systems. Please refer also to Chapter IV for the testing strategy on biodegradation.

(a) Aerobic aquatic degradation study (ADS)
Test according to OECD Test Guideline 309 (Aerobic Mineralisation in Surface Water – Simulation Biodegradation Test), ISO method 14592 or US-EPA guideline OPPTS 835.3100 with non-adapted inoculum.

(b) Water/sediment degradation test (ADS)
Usually a water/sediment degradation test under aerobic conditions is required. A water/sediment degradation study under anaerobic conditions should be done if the exposure of the substance to anaerobic conditions is very likely (e.g. when a major proportion of the substance is absorbed in sediment).

Test according to EC method C.24 (Aerobic and Anaerobic Transformation in Aquatic Sediment Systems) or corresponding OECD Test Guideline 308 (Aerobic and Anaerobic Transformation in Aquatic Sediment Systems).

Amounts of metabolites found in the water and the sediment phase shall be added up for the identification of relevant metabolites.

10.1.3.3. Biodegradation in sea water (ADS)

If a substance is to be used or released in marine environments in considerable amounts (e.g. it is known to be repeatedly used or continuously released in marine environments), then a seawater biodegradation test according to OECD Test Guideline 306 (Biodegradability in Seawater) will be required.

A modified version of ISO 14592 (shake flask batch test) with seawater at environmentally relevant concentrations may be performed (radio-labelled).

Alternatively, a water/sediment degradation study in seawater according to modified guidelines may be done.

10.1.3.4. Biodegradation during manure storage (ADS)

A study on biodegradation in manure is needed for substances which are applied in animal housings and go to manure storage before release to the environment. This is probably the case with veterinary hygiene biocidal products and biocidal pest control products. Please refer also to Chapters IV Testing Strategy and V Product-type-specific data set.

For the time being, there is no harmonised guideline for testing biodegradation in manure storage systems. Meanwhile zero degradation in manure may be taken into account in a first tier assessment.

Please contact ECHA or the evaluating Member State competent authority to discuss concretely how to perform a respective study. An OECD test guideline is under development.

10.1.4. Adsorption and desorption in water/aquatic sediment systems and, where relevant, adsorption and desorption of metabolites and degradation products (ADS)

This information is relevant for substances or transformation products that are released directly or indirectly to water/sediment systems. Please refer also to Chapter II Section 10.1.2.

In addition to the tests described there, a specific study with sediments or sewage sludge may be provided to refine the initial risk assessment, if adsorption to it is of concern.

These tests should be conducted as a full test (tier 3) according to EC method C.18 (Adsorption/Desorption Using a Batch Equilibrium Method) or the corresponding OECD Test Guideline 106 (Adsorption - Desorption Using a Batch Equilibrium Method) with sediments, or with sludge, for example according to US-EPA guideline OPPTS 835.1110 (Activated sludge sorption isotherm); or according to EC method C.24 (Aerobic and Anaerobic Transformation in Aquatic Sediment Systems) or the corresponding OECD Test Guideline 308 (Aerobic or Anaerobic Transformation in Aquatic Systems).

Please also refer to the testing strategy in Chapter IV.

10.1.5. Field study on accumulation in the sediment (ADS)

Field studies on accumulation in the sediment would be required in two sediment types if the $DT_{90field}$ > one year and the $DT_{50field}$ > three months, or if during laboratory tests non-extractable residues are formed in amounts > 70% of the initial dose after 100 days with a mineralisation rate of < 5% in 100 days. As it is not expected that these triggers will be met, it is assumed that such studies would not be provided. Furthermore the results could not be used to refine the risk assessment. Anyhow, no standardised test guideline is currently available. Some general guidance is available from SETAC (SETAC, 1995).

10.1.6. Inorganic substances: information on fate and behaviour in water (ADS)

For the moment there is no harmonised guideline addressing this endpoint.

10.2. Fate and behaviour in soil (ADS)

Tests on fate and behaviour in soil only become necessary if there is exposure to soil.

If the results from tests specified under Chapter II Sections 10.1.1.2a or 10.1.1.2b of the data set for the active substance indicate the need to do so or the active substance has an overall low or absent abiotic degradation, then the tests described under Chapter II Section 10.2 in the following paragraphs are required.

The data submitted under this paragraph should clarify, in addition to the degradation of the substance, other relevant routes of dissipation in soil, such as volatilisation, leaching and

transformation into bound residues. The testing strategy on biodegradation of biocidal active substances (see Figure 5 and text in Chapter IV) provides more specific information.

10.2.1. Laboratory study on rate and route of degradation (ADS)

including identification of the processes involved and identification of any metabolites and degradation products in one soil type (unless pH dependent route) under appropriate conditions. Laboratory studies on rate of degradation in three additional soil types.

The rate and route of aerobic degradation should be studied in one soil type for ≥ 100 days including identification of the processes involved and identification of major metabolites, degradation products and bound residues under appropriate conditions. The criteria for selection of suitable soil types should address the physico-chemical properties of the substance itself (e.g. pK_a). If there is reason to believe that the route of degradation is pH dependent, the route of degradation should be reported for at least one additional soil with a different pH value. The study can be of shorter duration if the required results are already available.

The rate of aerobic degradation should be investigated in three additional soil types for the active substance and for major metabolites. If the degradation rate for the metabolite(s) can be determined from the study on the active substance, there is no need to perform separate studies for the metabolite(s). The study should provide the best possible estimates of the time taken for degradations of 50% ($DegT_{50lab}$) of a substance under more relevant environmental conditions than those of a test on ready or inherent biodegradation.

These tests should be conducted according to EC method C.23 (Aerobic and Anaerobic Transformation in Soil) or the corresponding OECD Test Guideline 307 (Aerobic and Anaerobic Transformation in Soil) or OECD Test Guideline 304A (Inherent Biodegradability Test in Soil). If the results show that bound residues may amount to > 10%, they should be characterised (see Chapter II Section 10.2.7).

10.2.2. Field studies, two soil types (ADS)

Soil dissipation studies have to be conducted for the active substance, major metabolites, degradation and reaction products in those conditions where $PEC/PNEC_{soils} > 1$ **and**

- the $DegT_{50lab}$ > 60 days in one or more soils, determined at 20 °C at a moisture content of the soil related to a pF value of 2 (suction pressure) **or**
- the $DegT_{90lab}$ > 200 days in one or more soils, determined at 20 °C at a moisture content of the soil related to a pF value of 2 (suction pressure) is greater than 200 days.

If there is danger for the groundwater, the result of this study can be used to refine the preliminary risk assessment.

Further guidance on the degradation and transformation parameters of the active substance/metabolite is provided in FOCUS Groundwater (EU, 2002a)and FOCUS Degradation Kinetics (EU, 2011d).

The soil dissipation studies should provide estimates of the time taken for dissipation of 50% and 90% (DT_{50} and DT_{90}) and if possible the time taken for degradation of 50% and 90% ($DegT_{50}$ and $DegT_{90}$) of the active substance under field conditions. Where relevant, information on metabolites, degradation and reaction products must be reported.

Individual studies on a range of representative soils (in contrast to what is stated in Annex II of the BPR, the information should normally be provided for four different types) must be continued

until > 90% of the amount applied has dissipated. The maximum duration of the studies is normally 24 months.

Field studies must cover representative test conditions for the respective emission in use as a biocide (e.g. injection of contaminated STP sludge, contaminated manure, leaching from artificial matrix like paint or spray application, where relevant).

Test according to NAFTA Regulatory Directive - DIR2006-01 Guidance Document for Conducting Terrestrial Field Dissipation Studies (NAFTA, 2006).

10.2.3. Soil accumulation studies (ADS)

Field soil accumulation tests are required in two soil types if the $DisT_{90field}$ > one year and the $DisT_{50field}$ > three months, or if during laboratory tests non-extractable residues are formed in amounts > 70% of the initial dose after 100 days with a mineralisation rate of < 5% in 100 days.

The tests should provide sufficient data to evaluate the possibility of the accumulation of the active substance and of its transformation products in soil.

No standardised test guideline is currently available. Some general guidance is available from (Boethling, et al., 2009).

10.2.4. Adsorption and desorption in at least three soil types and, where relevant, adsorption and desorption of metabolites and degradation products (ADS)

This information is relevant for substances or transformation products that are released directly or indirectly to soil.

Please refer also to Chapter II Section 10.1.2. In addition to the tests described there, a full scale study (isotherms, mass balance, desorption) with soil needs to be provided in case of direct exposure to soil of a substance unless it is shown to be readily biodegradable.

A full scale adsorption test may also be appropriate to refine the PEC value in those cases where:

- PEC/PNEC > 1 as a result from indirect exposure (e.g. spreading of contaminated sewage sludge on land) and the substance is not readily biodegradable,
- modelling results indicate that relevant concentrations of the substance may reach groundwater (Council Directive 98/83/EC).

Full test (tier 3) according to EC method C.18 (Adsorption/Desorption Using a Batch Equilibrium Method) or the corresponding OECD Test Guideline 106 (Adsorption/desorption Using a Batch Equilibrium Method) with soils. The criteria for the selection of suitable soil types should address the physico-chemical properties of the substance itself (e.g. pK_a).

The testing strategy in Chapter IV indicates when which sorption test is necessary to be provided.

10.2.5. Further studies on sorption (ADS)

Please refer to Section 10.1.2 of this chapter. The testing strategy in Chapter IV indicates when which sorption tests would be necessary.

10.2.6. Mobility in at least three soil types and, where relevant, mobility of metabolites and degradation products (ADS)

In most cases, the mobility of a substance in soil can be estimated by means of running mathematical model calculations, processing adsorption coefficient and degradation rates of the substance (and its transformation products) but also pedological and climatic parameters.

10.2.6.1. Column leaching studies (ADS)

Column leaching studies must be carried out where in the adsorption/desorption studies provided under the endpoint 10.2.4 it is not possible to obtain reliable adsorption coefficient values. Soil column leaching studies can provide reliable and useful lower limits of the K_{OC} if the expected K_{OC} value is less than about 25 L/kg.

The test should provide sufficient data to evaluate the mobility and leaching potential of the active substance.

Studies must be carried out in three to four soils (in accordance with the test guideline) with varying pH, organic carbon content and texture. At least three soils should have a pH at which the test substance is in its mobile form. During the test period, the soil leaching columns should be kept in the dark at an ambient temperature (18 and 25 °C) within a range of ±2 °C.

Test according to OECD Guidance Document 312 (Leaching in Soil Columns).

10.2.6.2. Lysimeter studies (ADS)

Where it is indicated from data on adsorption and degradation in soil that relevant amounts of a substance may reach groundwater it may become necessary to carry out an outdoor confirmatory study. For guidance on how to perform a long term study on mobility of a substance in undisturbed soil under outdoor conditions refer to OECD Guidance Document 22 (Performance of Outdoor Monolith Lysimeter Studies).

10.2.6.3. Field leaching studies (ADS)

Similarly to Chapter II Section 10.2.6.2, follow OECD Test Guideline 22 (Performance of Outdoor Monolith Lysimeter Studies).

10.2.7. Extent and nature of bound residues (ADS)

The determination and characteristics of bound residues is recommended to be combined with a soil simulation study.

Required if the results of soil simulation studies (Chapter II Section 10.2.1) indicate that bound residues may be formed which account for more than 10% of the active substance added. Testing should be done according to SETAC procedures (SETAC, 1995) with a radio-labelled active substance and the nature of the bound residues should be characterised as far as possible according to, for example, (Schnitzer, 1982) or after an acetone/methanol-ultrasonic treatment according to OECD Test Guideline 304A (Inherent Biodegradability in Soil).

The unavailability of bound residues should be thoroughly investigated using different solvents.

Further Guidance:

- DG-AGRI Guidance Document on Persistence in Soil (EU, 2000c)

- Environmental Persistence of Organic Pollutants: Guidance for Development and Review of POP Risk Profiles (Boethling, et al., 2009)

10.2.8. Other soil degradation studies (ADS)

Such further studies should identify rates of degradation in different release conditions and main routes of degradation in soil in detail. Any major metabolites (or other degradation products that at any sampling time during the studies account for more than 10% of the active substance added) should be identified and their degradation rates should be studied. For example, a soil photolysis study is required where the deposition of the active substance at the soil surface is significant (e.g. is over 10% of the substance applied) on the basis of results under endpoint 10.1.1.1b, the data set for the active substance and photolysis is considered to be a major way of degradation.

An anaerobic soil degradation study according to e.g. EC method C.23 (Aerobic and Anaerobic Transformation in Soil) or the corresponding OECD Test Guideline 307 (Aerobic and Anaerobic Transformation in Soil) is required for one soil if exposure to anaerobic conditions is likely where the active substance or material treated with it is used. The general guidance for the corresponding data requirement for an aerobic degradation study (Chapter II Section 10.2.1) applies here also.

10.2.9. Inorganic substances: information on fate and behaviour in soil (ADS)

Main issues for the fate of inorganics are the adsorption and desorption and aging of these substances in the soil matrix. This information is relevant for substances or transformation products that are released directly or indirectly to soil (or to surface water). Bioavailability of metals is highly influenced by soil pH, the content of Fe and Al oxyhydroxydes, soil organic matter, and least importantly by the soil clay mineral content. Background metals are generally reduced in bioavailability as a result of aging in soils (or sediments), or transformation to less bioavailable salts. It seems that aging reactions are almost over after about one year and are reversible. At present, information regarding the aging reactions of different metals and metalloids, and sorbing solids, is very limited, so it is not possible to generalise which metals age at the fastest rate or with greater/less reversibility.

To derive adsorption coefficients for e.g. metals the total soil metal content and total metal pore water concentration of a wide geographical variety of *in situ* contaminated soils should be tested.

The principles in EC method C.18 (Adsorption/Desorption Using a Batch Equilibrium Method) or the corresponding OECD Test Guideline 106 (Adsorption - Desorption Using a Batch Equilibrium Method) also apply for inorganics.

Further Guidance:

- Evaluation and revision of Csoil parameter set RIVM report 711701021. (Otte, et al., 2001)
- Framework for Inorganic Metals Risk Assessment (External Review Draft) Section 4: Metal-Specific
- Topics and Methods (US EPA, 2004)

10.3. Fate and behaviour in air

10.3.1. Phototransformation in air (estimation method). Identification of transformation products

An estimation of the phototransformation of a substance is necessary to complete the risk assessment for any compound that is subject to ambient or artificial light. Although for some chemicals direct photolysis may be an important breakdown process, the most effective elimination process in the troposphere for most substances results from reactions with photochemical generated species like OH radicals, ozone and nitrate radicals. In a first approach, the specific first order degradation rate constant of a substance with OH-radicals can be estimated by (Q)SAR methods. Further details can be found in TGD (EU, 2003).

A qualitative discussion of the potential formation of breakdown products should be included.

Furthermore, an assessment of the global warming potential, the stratospheric ozone depletion potential, the potential for tropospheric ozone formation as well as the acidification potential should be submitted (part B of the BPR technical Guidance (guidance under development)).

Further Guidance:

Thesoftware AOPWIN™ estimates the gas-phase reaction rate for the reaction between the most prevalent atmospheric oxidant, hydroxyl radicals, and a chemical. In addition, AOPWIN™ informs if nitrate radical reaction will be important. Atmospheric half-lives for each chemical are automatically calculated using assumed average hydroxyl radical and ozone concentrations (http://www.epa.gov/opptintr/exposure/pubs/episuite.htm). It is integrated into the Estimation Programs Interface Suite (EPI Suite™) developed by the EPA's Office of Pollution Prevention Toxics and Syracuse Research Corporation (SRC).

10.3.2. Fate and behaviour in air, further studies (ADS)

If the active substance is to be used in preparations for fumigants or it has a hazard potential to the atmospheric environment, its degradation behaviour has to be determined experimentally (e.g. according to the methods described in (OECD, 1992). For the most important processes, the rate constants should first be estimated theoretically and then, after considering the relative importance of the various processes, confirmed experimentally.

For experimental estimation the data must be submitted for a purified active substance of stated specification.

The identification of transformation products which at any sampling time account for more than 10% of the active substance added is required unless the half-life of the transformation product is less than three hours.

The data submitted should be applicable to atmospheric conditions (light intensities, spectral distribution, etc.).

Further Guidance:

- Procedure for Assessing the Environmental Fate and Ecotoxicity of Pesticides (SETAC, 1995)

10.4. Additional studies on fate and behaviour in the environment (ADS)

No additional studies proposed.

10.5. Definition of the residue (ADS)

10.5.1. Definition of the residue for risk assessment (ADS)

Relevant components for the risk assessment are considered the parent substance and:

- all major metabolites in the relevant receiving compartments fresh- and marine water, sediment, STP influent/effluent, active sludge, soil, groundwater and air, or
- all metabolites that pose a comparable or higher hazard than the active substance.

Further Guidance:

- OECD Guidance Document on the Definition of Residue (OECD, 2006)

10.5.2. Definition of the residue for monitoring (ADS)

The worst case principle is that the parent and metabolites considered relevant for risk assessment (see Chapter II Section 10.5.1) are also relevant for monitoring. Waiving of this requirement is possible:

- by identifying those components in the residue that are most representative for all other components
- on basis of the (non-)concern of a metabolite identified in the risk assessment.

This may differ between the receiving compartments freshwater and marine, sediment, STP influent/effluent, active sludge, soil, groundwater, and air.

10.6. Monitoring data (ADS)

The worst case principle is that the parent and metabolites considered relevant for risk assessment (see Chapter II Section 10.5.1) are also relevant for monitoring. Waiving of this requirement is possible:

- by identifying those components in the residue that are most representative for all other components
- on basis of the (non-)concern of a metabolite identified in the risk assessment.

This may differ between the receiving compartments freshwater and marine, sediment, STP influent/effluent, active sludge, soil, groundwater, and air.

10.6.1. Identification of all degradation products (>10%) must be included in the studies on degradation in soil, water and sediments (ADS)

In contrast to what is stated in Annex II of the BPR, metabolites according to the definition given in Chapter I Section 1.6 need to be identified.

Further Guidance:

- Chapter R.7b: Endpoint specific guidance R.7.9.5 Conclusions for degradation/biodegradation (ECHA, 2012c)
- Chapter R.7c: Endpoint specific guidance R.7.10.3.3 Field data on aquatic bioaccumulation, (ECHA, 2012c)
- Important information on the use of monitoring data in the environmental exposure assessment is given in Chapter 2.2 of Part II of the TGD (EU, 2003).

11. Measures necessary to protect human health, animals and the environment

11.1. Recommended methods and precautions concerning handling, use, storage, transport or fire

Provide technical safety precautions and where exposure cannot be prevented by other means, application of personal protective equipment (PPE) when handling the active substance, e.g. during different stages of the process, to minimise the risk of exposure to humans and the environment.

As specified in point 62 of Annex VI of the BPR, *the evaluating body shall, where appropriate, conclude the criterion (iii) under point (b) of Article 19(1) can only be complied with by application of prevention and protection measures including the design of work processes, engineering controls, use of adequate equipment and materials, application of collective protection measures including the wearing of personal protective equipment such as respirators, breathing-masks, overalls, gloves and goggles, in order to reduce exposure for professional operators.*

If sufficient ventilation is required, the ventilation rate must be specified (number of air changes per hour) and it must be explained how it can be achieved (e.g. window, air conditioning).

Concerning PPE, details on the description of the equipment should be provided for example:

- for gloves: information on the material, thickness, protection level (grade)
- for respiratory protection equipment: information on the type of mask (full, half, FFP, helmet, hood, mouthpiece) and the type and class of filter or SCBA
- for coverall: type and EN standard

Appropriate precautions for substances which are flammable, oxidising etc. should be given. Handling, storage and transport must take into account any surface which could directly or indirectly come into contact with the product, including for example: processing equipment, piping, ventilators, transport vehicles and their washing and cleaning, as well as protective clothing and shower areas for workers. Storage precautions should include ventilation system to be used for storerooms (in general terms and other conditions for storage, e.g. temperature regime). Precautionary measures during service should especially be considered in addition to the prevention of environmental effects and measures to be taken when the substance is released to the environment due to an accident and misuse.

Materials which are incompatible with the substance, e.g. substances and products which may react with the active substance evolving toxic gases, and also other dangers such as reactions resulting in a large increase in volume, aggressive acidity, the possibility of dust explosions etc. should be indicated.

The precise type of fire-fighting equipment (i.e. both the type of extinguishing agent, including those to be avoided and any protective equipment), e.g. water or carbon dioxide, should be noted.

11.2. In case of fire, nature of reaction products, combustion gases etc.

It should be stated what gases are evolved, either by experiment or on the basis of structure, when the substance burns or when heated in the absence of air so that it simply decomposes, e.g. nitrogen oxides, phosgene or soot.

Especially the identity of dangerous substances formed should be given (e.g. analysed according to the ISO standard 9122, Part 3).

11.3. Emergency measures in case of accident

Specific treatment in case of an accident, for example, first aid measures following accidental eye or skin contact, ingestion or inhalation, antidotes, medical treatment if available; emergency measures to protect the environment.

Provide precise medical data regarding first aid, proven antidotes, and proven medical treatment. This should detail the effectiveness of first aid, suggested antidote doses, etc. and include full documentation of reference sources. The information here is intended for the purpose of immediate first-aid treatment. It is not intended to replace definitive diagnosis and treatment, which can only be undertaken by a qualified medical doctor.

Measures and courses of action in response to different kinds of accident scenarios (e.g. threat of release of the biocidal product, the product is actually being released and release has already occurred) should be described. In addition, actions to avert or stop release, minimise impacts of release, protect human life and property, and recover the product and by-products should be indicated.

11.4. Possibility of destruction or decontamination following: (a) Air, (b) Water, including drinking water, and (c) Soil

This is on the prevention of health and environmental effects and measures to be taken when the product is released to the environment due to an accident or misuse.

Provide details of measures necessary to quickly limit the consequences of accidental release to the environment, and to decontaminate areas affected by the accidental release. These may include neutralisation, destruction and removal procedures.

11.5. Procedures for waste management of the active substance for industry or professional users

Provide information necessary for safe disposal including treated material. If preliminary treatment of the waste is necessary, information about this must also be provided. If any waste generated from the substance is classified as hazardous waste (e.g. according to Commission Decision 2000/532/EC), this has to be mentioned separately and appropriate handling according to the related legislation has to be indicated.

More information is provided in Chapter III Section 11.5.

11.6. Possibility of reuse or recycling

The possibility of recovery or recycling should be given for both normal uses of the substance and quantities involved in spills.

11.7. Possibility of neutralisation of effects

Neutralisation procedures (e.g. by reaction with an alkali to form less toxic compounds) for use, for instance, in the event of accidental spillage must be described where they are feasible. Details to be given: proposed procedures for small and large quantities, evaluation of products of

neutralisation (in small and large quantities), procedures for disposal of neutralised waste (in small and large quantities).

11.8. Conditions for controlled discharge including leakage qualities on disposal

e.g. controlled landfill or extensive dilution (to be specified) before discharge to surface water. If a controlled landfill is recommended for use as a disposal site, information about the necessary preliminary treatment, the fate of the waste in the landfill, the release of active substances or breakdown products from the waste etc. must be given.

11.9. Conditions for controlled incineration

If the suggested waste disposal method is incineration, the compounds generated by burning (e.g. whether polychlorinated dioxins and furans or other halogen compounds can be formed), recommended incineration conditions (temperature, reaction time and oxygen content) and other information needed for the safe incineration of the waste must be provided.

11.10. Identification of any substances falling within the scope of List I or List II of the Annex to Council Directive 80/68/EEC

of 17 December 1979 on the protection of groundwater against pollution caused by certain dangerous substances, of Annex I and II to Directive 2006/118/EC of the European Parliament and of the Council of 12 December 2006 on the protection of groundwater against pollution and deterioration, of Annex I to Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on environmental quality standards in the field of water policy, of Part B of Annex I to Directive 98/83/EC or Annex VIII and X to Directive 2000/60/EC

Substances that are listed in the respective Annexes of the following legal frameworks are considered hazardous substances and therefore need to be monitored. Specify if the active substance is listed in one of the following:

- Council Directive 80/68/EEC on the protection of groundwater against pollution caused by certain dangerous substances. All biocides and their derivatives are classed in either List I or II. Direct discharge of substances in List I is prohibited. Discharge of substances in List II must be limited. In addition other substances (additives, impurities) may fall within the scope of the Lists.

- Council Directive 2006/118/EC, the Groundwater Directive, establishes a regime which sets underground water quality standards and introduces measures to prevent or limit inputs of pollutants into groundwater. Annex I lists groundwater quality standards and Annex II lists threshold values for groundwater pollutants and indicators of pollution.

- Council Directive 2008/105/EC, also known as the Priority Substances Directive, which sets environmental quality standards (EQS) for the substances in surface waters (river, lake, transitional and coastal) and confirmed their designation as priority or priority hazardous substances, the latter being a subset of particular concern. Annex I represents a list of priority substances.

- Council Directive 98/83/EC concerns the quality of water intended for human consumption. It aims at protecting human health from the adverse effects of any contamination of water intended for human consumption by ensuring that it is wholesome and clean. Chemical quality standards are specified in Annex I.

- Directive 2000/60/EC is the EU Water Framework Directive. Annex VIII lists the main pollutants. Annex X lists water policy priority substances and 'priority hazardous substances'.

12. Classification, labelling and packaging

Hazard classification is a process involving identification of the physical, health and environmental hazards of a substance (or a mixture), followed by comparison of those hazards (including degree of hazard) with defined criteria in order to arrive at a classification of the substance (or mixture). The classification criteria are defined in Annex I to CLP Regulation and – until 1 June 2015 - in Annex VI of Directive 67/548/EEC.

Active substances are normally subject to harmonised classification and labelling for all hazard classes (consult the Guidance documents on the application of Regulation (EC) No 1272/2008). In the sections below guidance is given on how the applicant should report existing harmonised classification and labelling or propose one. Following the assessment during the evaluation of the application, the evaluating competent authority (but not the applicant) will prepare and submit the proposal for the harmonised classification and labelling of the active substance to the Agency (Articles 36(2) and 37 of CLP). It advisable that the evaluating competent authority consults ECHA as early as possible to get the best support and advice in preparing the proposal.

12.1. State any existing classification and labelling.

If available, state the existing classification and labelling as provided in Part 3 of Annex VI of CLP, which contains lists of harmonised classifications and labelling of hazardous substances. If there is no harmonised classification for some/all endpoints or there is new information which may justify changing the existing harmonised classification, proceed to endpoint 12.2 below.

12.2. The hazard classification of the substance resulting from the application of Regulation (EC) No 1272/2008

In addition, for each entry, the reasons why no classification is given for an endpoint should be provided.

Propose hazard classification, labelling and packaging in line with CLP criteria if no harmonised classification and labelling is provided in Part 3 of Annex VI of CLP or if the new information justifies revision of the harmonised classification and labelling for a given endpoint. The need for classification should be considered based on relevant available information. CLP Regulation does not require new testing for the purpose of classification for health or environmental hazards (Article 8(1) of CLP); testing for the purposes of determining whether the substances entails any of the physical hazards referred to in part 2 of Annex I to CLP, tests required in that Part are necessary unless adequate and reliable information is already available (Article 8(2) of CLP). The background information should be clearly presented in the relevant sections of the dossier (see Chapter II, Sections 4, 8, 9 and 10).

12.2.1. Hazard Classification

A substance (or a mixture) that fulfils the criteria relating to physical hazards, health hazards or environmental hazards, laid down in Parts 2 to 5 of Annex I to CLP is hazardous and must be classified in relation to the respective hazard classes provided for in that Annex.

For further information on the classification criteria refer to Guidance on the application of the CLP criteria (ECHA, 2012a).

12.2.2. Hazard pictogram

A substance (or mixture) classified as hazardous must bear a label which includes relevant hazard pictograms in accordance with Article 19 of CLP, where applicable.

For further information on the hazard pictograms refer to **Chapter 4.3 Hazard Pictograms** in the Guidance document on Labelling and Packaging in accordance with Regulation (EC) No 1272/2008 (ECHA, 2011b).

Pictograms can be downloaded free of charge from the web page:
http://www.unece.org/trans/danger/publi/ghs/pictograms.html.

12.2.3. Signal word

A substance (or mixture) classified as hazardous must bear a label which includes a relevant signal word in accordance with Article 20 of CLP, where applicable.

For further information on the signal word please refer to **Chapter 4.4 Signal Words** in the Guidance document on Labelling and Packaging in accordance with Regulation (EC) No 1272/2008 (ECHA, 2011b).

12.2.4. Hazard statements

A substance (or mixture) classified as hazardous must bear a label which includes the relevant hazard statements in accordance with Article 21 of CLP, where applicable.

For further information on the hazard statements please refer to **Chapter 4.5 Hazard statement** in the Guidance document on Labelling and Packaging in accordance with Regulation (EC) No 1272/2008 (ECHA, 2011b).

A substance (or mixture) classified as hazardous must bear a label which includes relevant supplemental hazard information in accordance with Article 25 of CLP, where applicable.

For further information on the supplemental hazard information please refer to **Chapter 4.8 Supplemental labelling information** in the Guidance document on Labelling and Packaging in accordance with Regulation (EC) No 1272/2008 (ECHA, 2011b).

12.2.5. Precautionary statements including prevention, response, storage and disposal

A substance (or mixture) classified as hazardous must bear a label which includes relevant precautionary statements in accordance with Article 22 of CLP, where applicable.

Annex I and Annex IV of CLP outline the types of precautionary statements.

For further information on the precautionary statements please refer to **Chapter 4.6 Precautionary Statements** in the Guidance document on Labelling and Packaging in accordance with Regulation (EC) No 1272/2008 (ECHA, 2011b).

12.3. Specific concentration limits, where applicable, resulting from the application of Regulation 1272/2008

Specific concentration limits and M-factors for classification of substances and mixtures must be set, where applicable.

Article 37 of CLP rules out the procedures for submitting a proposal for harmonisation of classification and labelling of substances to ECHA together with, where appropriate, specific concentration limits or M-factors.

Section 1.1.2.3 of Annex VI of CLP provides further information on specific concentration limits and M-factors.

13. Summary and evaluation

The key information identified from the endpoints in each sub-section (2-12) is summarised, evaluated and a draft risk assessment is performed.

The summary and evaluation must be provided in separate assessment documents attached to the IUCLID file (the templates will be available on the ECHA website).

III. DOSSIER REQUIREMENTS PRODUCT

1. Applicant

Applications for authorisation of a biocidal product may be made by, or on behalf of, prospective authorisation holders.

1.1. Name and address

Name and address of the natural or legal entity of the applicant and prospective authorisation holder, if different.

1.2. Contact person

Names, address, telephone and fax numbers, email, and other contact information of the applicant and prospective authorisation holder, if different.

The authorisation holder is required to have a permanent office with a legally responsible representative within the territory of the European Union.

1.3. Manufacturer and formulator of the biocidal product and the active substance(s) (names, addresses, including location of plant(s))

- Name, address and location of manufacturing plant(s).

2. Identity of the biocidal product

The information must be sufficient to identify the biocidal product, to define it in terms of its specification and to characterise it in terms of its nature. The information submitted should, in any case, be sufficient to support a risk assessment demonstrating that the criteria referred to in BPR Article 19 are met. BPR Article 3(1)(a) defines 'biocidal product' as:

- *any substance or mixture, in the form in which it is supplied to the user, consisting of, containing or generating one or more active substances, with the intention of destroying, deterring, rendering harmless, preventing the action of, or otherwise exerting a controlling effect on, any harmful organism by any means other than mere physical or mechanical action,*
- *any substance or mixture, generated from substances or mixtures which do not themselves fall under the first indent, to be used with the intention of destroying, deterring, rendering harmless, preventing the action of, or otherwise exerting a controlling effect on, any harmful organism by any means other than mere physical or mechanical action.*

2.1. Trade name or proposed trade name

If different trade names are used in different Member States, all of those have to be cited.

2.2. Manufacturer's development code and number of the product, if appropriate

Company(ies) code number(s) or internal name(s).

2.3. Complete quantitative (g/kg, g/l or % w/w (v/v) composition of the biocidal product

i.e. declaration of all active substances and non-active substances (substance or mixture according to Article 3 of Regulation (EC) No 1907/2006), which are intentionally added to the biocidal product (formulation) as well as detailed quantitative and qualitative information on the composition of the active substance(s) contained. For non-active substances, a safety data sheet in compliance with Article 31 of regulation (EC) No 1907/2006 has to be provided. In addition, all relevant information on individual ingredients, their function and, in case of a reaction mixture, the final composition of the biocidal product shall be given.

It is recognised that the active content will vary from batch to batch on manufacture and as a result of sampling and analytical errors. To account for these variations the following general limits should be applied to the active substance content at the point of manufacture:

Table 4 Tolerance limits of the active substance content at the point of manufacture

Declared nominal content of active in g/kg or g/L	Tolerance limit
Up to 25	±15% of the declared nominal content for homogenous formulations (e.g. emulsifiable concentrates, soluble concentrates, aqueous suspension concentrates) ±25% of the declared content for non-homogenous preparations (e.g. granules, water dispersible granules)
Above 25 up to 100	±10% of the declared nominal content
Above 100 up to 250	±6% of the declared nominal content
Above 250 up to 500	±5% of the declared nominal content
Above 500	±25 g/kg or g/L of the declared nominal content

For dilute products or heterogeneous products then alternative limits can be specified but must be justified.

The following information must be provided:

- Information on individual ingredients before mixing and the final composition of the product;
- The chemical name of each ingredient according to IUPAC or CA and their content in the product (g/kg) as well as trade names:
- CAS number and EC number (EINECS, ELINCS or No Longer Polymer List number);
- Structure or structural formula;
- Functions of the ingredients (e.g. solvent, stabiliser);
- Classification of components according to Directive 67/548/EEC for the components or classification of preparations according to Directive 88/379/EEC amended by 1999/45/EC, as appropriate;
- Classification of components or mixtures according to Regulation (EC) No 1272/2008 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), as appropriate;
- Indication of any substances of concern.

If a non-active ingredient is a preparation, full quantitative and qualitative specification of this preparation must be provided.

Further Guidance:

- ECHA Guidance for identification and naming of substances under REACH and CLP, (ECHA, 2012b)

2.4. Formulation type and nature of the biocidal product, e.g. emulsifiable concentrate, wettable powder, solution

Further Guidance:

- Manual on development and use of FAO and WHO specifications for pesticides, second revision, (FAO, 2010).
- ECHA Guidance for identification and naming of substances under REACH and CLP, Chapter 4.3.1.1 Information on chemical composition, (ECHA, 2012b).

3. Physical, chemical and technical properties

Data must be provided to demonstrate that the physical, chemical and technical properties of the formulation will be acceptable and that in use the biocidal product under practical conditions will result in an acceptable performance.

For further Guidance, see the Evaluation manual (EU, 2012a) and the FAO manual (FAO, 2010).

3.1. Appearance (at 20 °C and 101.3 kPa)

Please follow guidance in Chapter II Section 3.1.1.

3.1.1. Physical state (at 20 °C and 101.3 kPa)

Please follow guidance in Chapter II Section 3.1.1.

3.1.2. Colour (at 20 °C and 101.3 kPa)

Please follow guidance in Chapter II Section 3.1.3.

3.1.3. Odour (at 20 °C and 101.3 kPa)

Please follow guidance in Chapter II Section 3.1.4.

3.2. Acidity/alkalinity

The test is applicable when the pH of the biocidal product or its dispersion in water (1%) is outside the pH range 4-10.

In the case of aqueous biocidal products, the pH value of the biocidal product as formulated should be determined and reported. In the case of solid and non-aqueous liquid biocidal products which are to be applied as aqueous dilutions or dispersions the pH of a 1 % dilution or dispersion of the biocidal product should be determined and reported. Test according to CIPAC method MT 75.3.

The acidity/alkalinity must be determined when the pH of the biocidal product as formulated or its 1% dilution or dispersion is < 4 or >10. The acidity/alkalinity should be determined using CIPAC method MT 31. Alternatively, test according to CIPAC method MT 191.

Test according to the OECD Test Guideline 'Determination of pH, Acidity and Alkalinity' which is currently being developed.

3.3. Relative density (liquids) and bulk, tap density (solids)

In contrast to what is stated in Annex II of the BPR, the relative density should be determined in gases, liquids and solids. Please follow the guidance in Chapter II Section 3.5. The bulk and tap density can only be determined in solids. The recommended method is OECD Test Guideline 109 (Density of Liquids and Solids), updated in October 2012. This update includes bulk and tap density for solids, based on the CIPAC method MT 186 (Bulk density). Please note that OECD Test Guideline 109 (Density of Liquids and Solids) can also be used for testing the relative density (as already stated in Chapter II Section 3.5).

3.4. Storage stability, stability and shelf-life

Data are required to demonstrate that the biocidal product is stable on storage under the conditions and for the shelf life claimed for the product.

3.4.1. Storage stability tests

3.4.1.1. Accelerated storage test

The relevant test method is CIPAC method MT 46.3 (storage at 54 °C for two weeks).

Accelerated storage data generated can be used to give an indication that the biocidal product will be stable for two years at ambient temperature. These data can be used to demonstrate that the product is likely to be stable for two years at ambient storage to support an authorisation. Yet, this does not negate the need to generate ambient storage data, which must be generated to confirm the ambient storage of the biocidal product.

The accelerated storage stability test does not necessarily have to be conducted in the sales packaging. As outlined in CIPAC method MT 46.3, the accelerated storage study could be conducted in a glass jar.

The data also give an indication of the stability of the biocidal product if for intermittent periods it was subject to higher than normal temperatures. If it can be clearly demonstrated that the biocidal product will not be subjected to temperatures above 30^0C during storage then accelerated storage data will not be required provided that a full ambient storage study has been provided. Appropriate label phrases will be required to indicate that the biocidal product must not be stored at higher temperatures.

If the active is heat sensitive then the following conditions can be used to generate accelerated storage data:

Table 5 Conditions for accelerated storage testing for heat sensitive active substances

Temperature (±2°C)	Time (weeks)
54	2
50	4
45	6
40	8
35	12
30	18

3.4.1.2. Long term storage test at ambient temperature

Data must be generated in the worst case commercial packaging to support the ambient storage of the product for the claimed shelf life.

It is recognised that generating ambient storage data to support a shelf life of greater than two years may be problematic. To support these longer shelf life claims then, in general, an ambient storage study for two years should be provided along with relevant quality control data that assesses key parameters prior to and after storage for the required shelf life. The following information/data must be provided with the quality control data:

- Details of the storage conditions (length of storage, temperature and details of packaging the product has been stored in);
- Details and supporting validation data used to determine the active content (to be reported under Chapter III Section 5.1); and
- Justification of the physical chemical and technical properties determined in the QC data and how this supports the stability of the product.

For formulations that can be categorised according to the formulation types as included in revision 2 of the FAO manual (Manual on development and use of FAO and WHO specification for pesticides – November 2010 (FAO, 2010)), primarily, GIFAP (Croplife International) monograph no. 17 (Croplife, 2009) is the leading Guidance. Information on the relevant physical, chemical and technical properties for different formulation types is outlined in the Evaluation manual (EU, 2012a) and the FAO manual (FAO, 2010).

For all proposed packaging types, packaging suitability should be addressed.

Guidance is not yet available for all types of biocides e.g. for product-type 21 and product-type 6.

3.4.1.3. Low temperature stability test (liquids)

The relevant test method is CIPAC method MT 39.3.
The stability of the product on storage at 0°C for seven days should be addressed.

If the label gives clear instructions that the product must not be stored under conditions of ≤ 0°C (e.g. a phrase like 'protect from frost' on the label) then the low temperature storage does not need to be addressed.

For some formulation types the stability on freeze/thaw cycles may have to be investigated.

3.4.2. Effects on content of the active substance and technical characteristics of the biocidal product

In the storage stability studies the active substance content, relevant physical and chemical properties (e.g. pH) and relevant technical properties must be determined prior to and after storage.

Where relevant the effects of light, temperature and humidity must be investigated as part of the storage stability studies.

For the ambient storage studies, the biocidal product must be stored in the worst case commercial packaging and the stability of the packaging must be assessed. This should include observations on the appearance of the packaging and an assessment of the weight change on storage.

In these studies a storage in the worst case packaging is representative for the other commercial packaging. An assessment of all packaging types must be made. In general, the product should be stored in the worst case packaging and the relevance of these data to the other packaging types specified must be clearly outlined. Acceptable extrapolations for different packaging types are outlined below:

Table 6 Acceptable extrapolations for different packaging types for storage stability studies

Packaging used in shelf life study	Acceptable extrapolations
Water based formulations e.g aqueous suspension concentrates,soluble concentrates	
Any, except metal	All packaging types, apart from metal are supported with no further data
Solvent based formulations e.g. emulsifiable concentrates	
HDPE	HDPE/EVOH, HDPE/F, HDPE/PA packs would all be supported without further data
HDPE/EVOH or HDPE/F or HDPE/PA	Data generated in one of these three packaging will support authorisation in the other two packagings with acceptable seepage data in the required packaging HDPE packs would be supported with acceptable seepage data

Seepage data

Data are only required to demonstrate that the required packaging is stable for the required shelf life (e.g. no leakage, no ballooning, no panelling of the packaging, no deformations) rather than a new shelf life study in which all chemical and physical properties are investigated prior to and after storage. The weight change on storage should also be determined.

Where seepage is observed then the new packaging cannot be authorised. Any panelling and/or ballooning in the new packaging is an indication that the new packaging is not fully resistant to the formulation and/or air entrainment. In such cases, to ensure no adverse effects on the physical and chemical properties of the biocidal product then a complete shelf life study conducted in the new packaging will be required.

Solid preparations

Extrapolation to all types of packaging is acceptable except to more flexible packs. For solid formulations sold in flexible packs the effects of stacking on the packaging and the physical and

chemical properties must be investigated. The stacking undertaken must reflect those encountered in commercial practice.

Trigger sprayers
For ready for use biocidal products applied via a trigger sprayer then the satisfactory operation of the trigger sprayer prior to and after storage should be addressed. This should include the spray pattern, the amount of spray delivered with each operation and observations on the nozzle for blockages. Where the product is stored with the trigger sprayer then the satisfactory operation should be addressed after storage. Where the biocidal product is not applied in one single operation then the intermittent use of the sprayer during the storage internal should also be addressed: the satisfactory operation of the sprayer following successive uses followed by storage of the biocidal product must reflect commercial practice and cover the stated shelf life.

The satisfactory operation of aerosols prior to and after storage should also be addressed.

The active substance content should be determined using a validated method of analysis. It is generally recognised that a decrease in the active content of ≤10 % should not adversely affect the efficacy and risk assessment of the product. Where the degradation of the active content is >10%, or in cases where a decrease of <10% may impact on the efficacy and/or the risk assessment, then a justification for the acceptability of the decrease should be provided. This may require an assessment of the degradation on the efficacy and risk assessment. The fate (degradation products) of the active substance may have to be assessed. Alternatively, a more appropriate shelf life, in which the degradation of the active content is considered acceptable, should be proposed. For this reason, particularly when the active is known to degrade, it is advantageous to perform ambient storage studies in which the active content is assessed at interim time periods.

Substances of concern and relevant impurities should be considered for inclusion in the storage stability/shelf life studies. The level of the substance of concern or relevant impurity prior to storage and after storage should be determined using a fully validated method of analysis.

In cases where the substance of concern or relevant impurity cannot possibly increase on manufacture or storage of the biocidal product then they do not need to be included in the storage stability/shelf life study. A justification outlining clearly why the substance of concern or relevant impurity has not been included in the storage stability/shelf life study should be provided.

The relevance of the levels of the substance of concern or relevant impurity, including where relevant changes observed on storage, in the biocidal product should be addressed.

Where a substance of concern or relevant impurity is determined on storage then it should be determined using a validated method of analysis.

Where relevant the retention of palatability should be addressed. Reference to the efficacy assessment is acceptable to address this requirement.

Where an aversive agent[10] is present in the product and the presence of the aversive agent has been referenced in the risk assessment then its stability on storage, using a validated method of analysis, must be assessed.

[10] An aversive agent is a substance which is added to a biocidal product with the intent of deterring or limiting its ingestion.

3.4.2.1. Light

This endpoint is addressed in Section 3.4.2.

3.4.2.2. Temperature and humidity

This endpoint is addressed in Section 3.4.2.

3.4.2.3. Reactivity towards container material

Please follow Guidance in Chapter III Sections 3.4.1 and 3.4.2.

3.5. Technical characteristics of the biocidal product

Technical characteristics applicable to the formulation type must be addressed. Where relevant these must be generated to cover the maximum and minimum in use concentrations specified for the biocidal product.

Information on the relevant physical, chemical and technical properties for different formulation types is outlined in the Evaluation manual (EU, 2012a) and the FAO manual (FAO, 2010).

3.5.1. Wettability

The relevant test method is CIPAC method MT 53.3.1.

Wettability is determined to ensure the preparation is readily wetted in use. The data are required for solid preparations which are to be dispersed in water.

The method as written describes the wetting of wettable powder preparations but it also applicable to water soluble powders, water soluble granules and water dispersible granules.

A preparation is considered acceptable if there is complete wetting in one minute without swirling. Where a preparation is outside this limit then evidence must be submitted demonstrating acceptable wetting on use of the biocidal product e.g. in the application equipment.

3.5.2. Suspensibility, spontaneity and dispersion stability

Applicability depends on the formulation type (nature) of the biocidal product.

Suspensibility
Test according to CIPAC method MT 15.1 for wettable powders, CIPAC method MT 161 for aqueous suspension concentrates, CIPAC method MT 168 for water dispersible granules, CIPAC method MT 177 for water dispersible powders (simplified method) and CIPAC method MT 184 for suspensibility of formulations forming suspensions on dilutions with water.

Suspensibility is determined to demonstrate that a sufficient amount of the active substance is suspended to give a homogeneous mixture during application. For the determination of suspensibility, chemical assay ('active' suspensibility) is the only fully reliable method to measure the mass of an active substance still in suspension.

However, gravimetric determination (total suspensibility) or solvent extraction determination may be used providing that these methods have been shown to give equivalent results to those of the chemical assay.

Where there is more than one insoluble active substance present in the preparation, chemical assay ('active' suspensibility) is the only acceptable method.

The test should be performed at the highest and lowest dilutions recommended for use of the preparation.

The mean measured active suspensibility must not be less than 60% or greater than 110%. Where a preparation is outside these limits then evidence must be submitted demonstrating that the preparation is homogeneous on application through appropriate application equipment e.g. determination of the active substance content in the spray at the beginning, middle and end of a spraying operation at the highest and lowest use rates on the label.

Spontaneity of dispersion and dispersion stability
Test according to CIPAC method MT 160 regarding suspension concentrates and CIPAC method MT 174 on the degree of dispersion of water dispersible granules.

The spontaneity of dispersion is determined to show the preparation is rapidly dispersed when diluted with water.

As for the determination of suspensibility, chemical assay is the only reliable means to measure the mass of an active substance in suspension.

However, gravimetric determination or solvent extraction determination may be used on a routine basis providing that these methods have been shown to give equivalent results to those of the chemical assay.

Where there is more than one insoluble active substance present in the preparation, chemical assay is the only acceptable method.

The mean measured minimum active suspensibility or dispersibility must not be less than 60% or greater than 105%. Where a preparation is outside these limits then evidence must be submitted demonstrating that the preparation is homogeneous on application.

3.5.3. Wet sieve analysis and dry sieve test

Applicability depends on the formulation type (nature) of the biocidal product.

Wet sieve test
Test according to CIPAC method MT 59.3 Wettable powders, suspension concentrates, capsule suspensions and CIPAC method MT 167 Wet sieving after dispersion of water dispersible granules, CIPAC method MT 179 Degree of dissolution and solution stability, CIPAC method MT 182 Wet sieve test with re-cycled water and CIPAC method MT 185 Wet sieve test.

The residue remaining on a sieve is determined after dispersion to ensure no unacceptable residue remains which cause the blockage of nozzles or filters on application equipment.
The test is applicable to wettable powders, suspension concentrates, water dispersible granules, aqueous capsule suspensions, dispersible concentrates, suspo-emulsions, water soluble granules and water soluble powders.

A maximum of 2% may be retained on a 75 mm sieve. Where a preparation is outside this limit then evidence must be submitted showing the preparation may be satisfactorily applied through appropriate application equipment with no blockages.

Dry sieve
Test according to CIPAC method MT 59.1 for dusts and CIPAC method MT 59.2 (MT 58) for granular formulations (GR).

The test is designed to determine the size distribution of dustable powders and granules for direct application to allow acceptable application.

For dustable powders, the active substance content of material remaining on the sieve must be determined to demonstrate there was no separation of the active substance from the carrier if > 5% of the preparation is retained on a 75 µm sieve. Not more than (0.005 x AI content in g/kg) % should be present as the AI in the residue on the sieve.

3.5.4. Emulsifiability, re-emulsifiability and emulsion stability

Applicability depends on the formulation type (nature) of the biocidal product.

The relevant test methods are CIPAC method MT 36.3 for 0.1 – 5% dilutions, CIPAC method MT 173 for 0.1% - 2% dilution, and CIPAC method MT 180 on Dispersion stability of suspo-emulsions. The data are required to determine whether a preparation forms and maintains a stable emulsion. Tests should be performed in CIPAC water A and D and at the highest and lowest concentrations recommended for use.

The emulsion generated under the conditions of MT 36.3 may be at maximum 2ml cream after 30 mins, trace of oil. If any separation is observed re-emulsification should be complete after 24 hours.

The emulsion generated under the conditions of MT 180 may be at maximum 2ml cream after 30 mins, trace of oil. If any separation is observed, re-emulsification should be complete after 24 hours.

The absorbance measured for the formulation under the conditions of MT 173 must between 95-105% after four hours.

Where a preparation is outside these limits then evidence must be submitted showing the preparation remains homogeneous when applied.

If more than a trace of oil separates consideration should be given to reformulation.

3.5.5. Disintegration time

The disintegration time is applicable to all products that are tablets and depend on disintegration of the tablet in a solvent (water) for optimal efficacy. Applicable to ST (water soluble tablets) and WT (water dispersible tablets) formulations.

There is no relevant standard method available.
The data should demonstrate the tablet disintegrates rapidly on addition to water and that the formulation is readily dispersed and no blockages occur in the application equipment on use. A maximum disintigration time is to be specified.

The specified disintegration time should be supported by a study showing the disintigration is achieved within the specified maximum time, and that the product is sufficiently dispersed. If continuous agitation is required, this should be specified on the instructions for use/label.

3.5.6. Particle size distribution, content of dust/fines attrition, friability

Particle size distribution
The particle size distribution of powder biocidal products and granules must be addressed. The data generated must be sufficient to categorise the formulation type and is required to demonstrate that the biocidal product can be successfully applied using the appropriate application equipment. The relevant test methods are as follows:

Size distribution (powders):
- CIPAC Method MT 187: Particle size analysis by laser diffraction

Nominal size range (granules):
- CIPAC Method MT 170: Dry sieve analysis of water dispersible granules
- CIPAC Method MT 187: Particle size analysis by laser diffraction

For all powder biocidal products and biocidal products that are applied in a manner that generates exposure to aerosols, particles or droplets then the MMAD (mass medium aerodynamic diameter) must be determined. The percentage of particles in mass with aerodynamic diameter <50 µm must be established. Information regarding suitable test methods is outlined in the ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance, R.7.1.14 Granulometry, (ECHA, 2012c).

Dust
The dust content of solid preparations (granules and powders) must be determined to ensure there is no unacceptable risk to operators or bystanders or potential for blockage of application equipment.

The dust content should be generated using the following test method:
- CIPAC Method MT 171: Dustiness of granular products

Where the apparent dust content is >1% (by weight), the particle size and nature of the dust must be investigated in order to evaluate the potential risk to operators and bystanders. Methods applicable for determining the particle size of the dust are outlined in the ECHA Guidance on information requirements and chemical safety assessment (ECHA, 2012c).

Where a granular material is described as 'dusty' then evidence is required that the material may be satisfactorily applied through application equipment.

Attrition, friability
Attrition is defined as the wearing away of the surface of a granule by friction or impact, particularly by granule-to-granule interaction.

Friability is defined as the tendency of a granule to crumble, breaking down into smaller particles. These data are required to determine whether a granular material is robust under normal conditions of use and transport.
The relevant test methods (applicable for granules or tablets) are:
- CIPAC Method MT 178: Attrition resistance of granules
- CIPAC Method MT 178.2: Attrition resistance of dispersible granules

Where the material has an attrition resistance of <98% then the particle size of the dust must be determined and the risk to operators and bystanders must be addressed. Information on assessing the particle size of the dust is outlined above.

Where the material has an attrition resistance of <98% then evidence is required that the material may be satisfactorily applied through the application equipment.

3.5.7. Persistent foaming

Applicability depends on the formulation type (nature) of the biocidal product. The data are required when the product is applied in water for use. The data are not required when the product is intended to be for foam application.
Persistent foam is determined to measure the amount of foam likely to be present in a spray tank or other application equipment following dilution of the preparation.

Although CIPAC method MT 47.2 was standardised for the determination of persistent foam in suspension concentrates it is also applicable to other preparations which are dispersed in water.

The test must be performed at the highest and lowest in use concentrations recommended for use.

The level of foam generated under the conditions of CIPAC method MT47.2 should not exceed 60ml after 1 minute. Where a preparation is outside these limits then evidence must be submitted showing that there is no unacceptable risk to operators following use of the preparation through the appropriate application equipment.

3.5.8. Flowability / Pourability / Dustability

Applicability depends on the formulation type (nature) of the biocidal product.

Flowability
The relevant test method is CIPAC method MT 172.

The data are required to demonstrate that granular materials remain free flowing after storage under pressure.

Data are only required for granular formulations applied through application equipment that would subject the granules to pressure and/or heat.

The method is not appropriate to those granules where water has been added as a formulant. For such granules alternative data to demonstrate that application through the equipment would be satisfactory must be provided.

The sample should flow through the sieve after a maximum of five liftings.

Pourability (rinsability)
The relevant test method is CIPAC method MT 148.

The data are required to demonstrate that the user can make use of the maximum amount of the preparation and that an excessive amount of the material does not remain in the container. The method is appropriate to suspension concentrates, capsule suspensions and suspoemulsions.

The residue observed with MT 148 should not exceed 5% residue and the rinsed residue should not be more than 0.25%.

The test can be performed in the commercial packaging using the recommended rinsing instructions if the standard lab test is failed.
Higher residues may cause hazardous situations during waste disposal. A justification is required on why high residues would not pose an issue or instructions should be provided on safe waste disposal.

Higher residues may also affect the ability to prepare the biocidal product at the maximum in use rate and hence adversely affect the efficacy. Appropriate evidence that the efficacy will not be adversely affected maybe required.

Dustability
The relevant test method is CIPAC method MT 34. However, the equipment used in this method is not readily available. Therefore, data are required showing the preparation may be satisfactorily applied as a dust through the proposed application equipment and that there is no unacceptable compaction or caking following a heat test under pressure.

3.5.9. Burning rate - smoke generators

Evidence is required that the preparation may be satisfactorily applied as a smoke and that the burning rate and burning completeness (see also Chapter III Section 3.5.10 and 3.5.11) support the proposed use. Where relevant the data must support intermittent use of the product.
The duration and burning rate of a smoke generator should be specified to establish how long it takes before the preparation stops generating smoke. A test is required, based on a representative in-use situation, to show the burning rate and duration comply with the specified rates.

The burning rate should correspond with the proposed use.

There is no relevant standard method available.

3.5.10. Burning completeness - smoke generators

Burning completeness must be determined by weighing the preparation before and after use. It should be demonstrated that by far the largest part of the active substance went up in smoke. This also requires determination of the concentration active substance in the residue.

There is no relevant standard method available.

3.5.11. Composition of smoke - smoke generators

The smoke composition must be analysed for the concentration of the active substance and decomposition products, if any, to guarantee that the produced smoke does indeed contain the active substance and no decomposition products.

There is no relevant standard method available.
The smoke should deliver the required active concentration and any decomposition products to be efficacious and the amount of active and any decomposition products should be supported by the toxicological and environmental risk assessments.

If, based on theoretical considerations, e.g. based on the endpoints provided for the active substance (degradation/combustion products after decomposition), or the heat generated during the generation of smoke is well below the decomposition temperature of the active substance and/or the absense of halogens or other compounds which may generate toxic fumes, a test may be waived.

3.5.12. Spraying pattern - aerosols

Homogeneity must be determined according to FEA method 644 (Filled Aerosols Packs – Evaluation of Aerosol Spray Patterns).

Spray diameter must be determined at 30 cm distance.

3.5.13. Other technical characteristics

Any other relevant technical characteristics that are not covered by this Guidance should be reported here.

3.6. Physical and chemical compatibility with other products including other biocidal products with which its use is to be authorised

Data to address the physical and chemical compatibility must be provided when label recommendations are made to co-apply the biocidal product with other substances, mixtures or biocidal or non-biocidal products (e.g. dyes).

If all properties of each component are known and it can be clearly demonstrated that a chemical reaction can be excluded then data to demonstrate the chemical compatibility will not be required.

Any known incompatibilities (physical and chemical) should be mentioned.

3.6.1. Physical compatibility

Possible physical incompatibility with any products should be mentioned.

Method ASTM E1518 (Standard Practice for Evaluation of Physical Compatibility of Pesticides in Aqueous Tank Mixtures by the Dynamic Shaker Method) can be used to investigate the physical compatibility.

3.6.2. Chemical compatibility

Possible chemical incompatibility with any products should be mentioned.

3.7. Degree of dissolution and dilution stability

Applicability depends on the formulation type (nature) of the biocidal product.

Degree of dissolution
The information is required for products used in a water soluble bag and for all tablets.
The dissolution rate should be demonstrated regarding tablets and products used in water soluble bags in water and that the formulation dissolves or disperses rapidly. The test should be performed at the highest concentration. As the greater the amount of solid to water the more difficult it will be to disperse.

The relevant test method is CIPAC method MT176 (water soluble bag). There is no specific method for tablets.

Dilution stability
The relevant test methods are CIPAC method MT 179 and MT41.

The dilution stability is determined to ensure that water-soluble preparations dissolve readily and/or, when diluted, produce stable solutions without precipitation, flocculation, etc. The results submitted should fully describe the appearance and amount of any separation or sediment.

The test should be conducted at the maximum in use concentration specified on the label.

For method MT 41, the acceptable limit would be a 'trace' of sediment after 30 minutes. For method MT 179, the amount of residue obtained on a 75 µm sieve should not exceed 2%. Where a preparation is outside this limit then evidence must be submitted showing the material separated will not block application equipment or present an unacceptable risk to the operator or affect the efficacy.

3.8. Surface tension

Test according to EC method A.5 (Surface Tension) and OECD Test Guideline 115 (Surface Tension of Aqueous Solutions).

For all liquid biocidal products the surface tension at the highest in use concentration recommended for use should be determined.

For liquid biocidal products containing ≥10% hydrocarbons and for which the kinematic viscosity is less than 7×10^{-6} m^2/sec at 40 °C the surface tension of the biocidal product as formulated should be determined at 25 °C.

For further Guidance see Chapter II Section 3.8.

Further Guidance:

- ECHA Guidance on information requirements and chemical safety assessment Chapter R7a: Endpoint specific guidance, R.7.1.6 Surface Tension, (ECHA, 2012c)

3.9. Viscosity

This data is always required for liquid formulations.

The viscosity should be determined at 20 °C and 40 ºC.

There is no relevant EC method. Test according to OECD Test Guideline 114 (Viscosity of Liquids), where the following determination methods are recommended:

- Capillary viscometer;
- Flowcup;
- Rotational viscometer;
- Rolling ball viscometer
- Drawing Ball Viscometer.

For liquid biocidal products containing ≥10% hydrocarbons and for which the kinematic viscosity is less than 7 x 10^{-6} m^2/sec at 40 °C the surface tension of the biocidal product as formulated should be determined at 25 °C.

Further Guidance:

- ECHA Guidance on information requirements and chemical safety assessment Chapter R7a: Endpoint specific guidance, R.7.1.18 Viscosity, (ECHA, 2012c)

4. Physical hazards and respective characteristics

The physical hazards of the biocidal products (endpoints 4.1 to 4.16, Annex III of the BPR), correspond to the physical hazards classes for mixtures included in the CLP Regulation. The criteria and testing methods or standards for each of these physical hazards required in the BPR are described in the corresponding section of Part 2 of Annex I to CLP Regulation.

For the purposes of determining whether a product entails any of the physical hazards referred to in Part 2 of Annex I to CLP: the manufacturer, importer or downstream user must perform the tests required by the above mentioned Part 2, unless there is adequate and reliable information available (Article 8(2), CLP). Furthermore, in this guidance for each relevant physical hazard a reference to the corresponding test according to UN Recommendations on the Transport and Dangerous Goods, Manual of Test and Criteria ,UN-MTC (UN, 2009), starting with an UN test method name is provided.

Further information can be found in the Guidance on the Application of the CLP Criteria (ECHA, 2012a).

4.1. Explosives

Please follow the guidance in Chapter II Section 4.1.

4.2. Flammable gases

Please follow the guidance in Chapter II Section 4.2.

4.3. Flammable aerosols

Please follow the guidance in Chapter II Section 4.3.

4.4. Oxidising gases

Please follow the guidance in Chapter II Section 4.4.

4.5. Gases under pressure

Please follow the guidance in Chapter II Section 4.5.

4.6. Flammable liquids

Please follow the guidance in Chapter II Section 4.6.

4.7. Flammable solids

Please follow the guidance in Chapter II Section 4.7.

4.8. Self-reactive substances and mixtures

Please follow the guidance in Chapter II Section 4.8.

4.9. Pyrophoric liquids

Please follow the guidance in Chapter II Section 4.9.

4.10. Pyrophoric solids

Please follow the guidance in Chapter II Section 4.10.

4.11. Self heating substances and mixtures

Please follow the guidance in Chapter II Section 4.11.

4.12. Substances and mixtures which in contact with water emit flammable gases

Please follow the guidance in Chapter II Section 4.12.

4.13. Oxidising liquids

Please follow the guidance in Chapter II Section 4.13.

4.14. Oxidising solids

Please follow the guidance in Chapter II Section 4.14.

4.15. Organic peroxides

Please follow the guidance in Chapter II Section 4.15.

4.16. Corrosive to metals

Please follow the guidance in Chapter II Section 4.16.

4.17. Additional physical indications of hazard

4.17.1. Auto-ignition temperatures of products (liquids and gases)

Please follow the guidance in Chapter II Section 4.17.1.

4.17.2. Relative self-ignition temperature for solids

Please follow the guidance in Chapter II Section 4.17.2.

4.17.3. Dust explosion hazard

Please follow the guidance in Chapter II Section 4.17.3.

5. Methods of detection and identification

Information on analytical methods is required for assessing compliance with conditions for issuing authorisation for a biocidal product. This information is also required for the post-authorisation control and monitoring purposes, and for the assessment of justifications which should be provided for the methods used for the generation of data as required in accordance with the BPR. If there are multiple active substances, an analytical method should be able to distinguish and individually quantify them. Validation of analytical methods does not have to be performed and reported to GLP. In particular cases where a specific analytical method cannot be developed, a common moiety approach or titration method may be acceptable.

Please also follow guidance in Chapter II Section 5.

Further Guidance:

- ECHA Guidance for identification and naming of substances under REACH; chapters 4.2.1.3. / 4.2.2.3. / 4.2.3.2., (ECHA, 2012b)

5.1. Analytical method including validation parameters for determining the concentration of the active substance(s), residues, relevant impurities and substances of concern in the biocidal product

The analytical method must be suitable to accurately determine the active substance content. In the case of a preparation containing more than one active substance, a method capable of determining each, in the presence of the other, should be provided. If a combined method is not submitted, the technical reasons must be stated.
Generally, linearity, specificity, recovery and repeatability should be addressed.

Linearity
See information for the technical material in Chapter II Section 5.1.

Specificity (Selectivity)
Example chromatograms from the analysis of a standard, sample and a blank formulation are required. The blank formulation should contain all the formulants and no active substance. Where the formulation contains two or more active substances and each has been determined using a separate method then adequate data must be provided to demonstrate that each active substance does not interfere with the determination of the others.

Repeatability
See information for the technical material in Chapter II Section 5.1.

Recovery (Accuracy)
The accuracy of the method should be reported as mean recovery for the pure active substance in the biocidal product. At least two recovery determinations should be made on representative samples containing a known quantity of the analyte. Samples should ideally be laboratory-prepared co-formulant mixes to which a known quantity of analyte is added and the whole sample analysed to reduce sampling error. However, where it is not possible to prepare a sample matrix without the presence of the analyte or there are difficulties in replicating the sample to be analysed (for example with pellet formulations), the standard addition method may be used.

The recovery data should meet the following requirements:

Table 7 Acceptable recovery values for residues or impurities

% active (nominal)	Mean % recovery
>10	98-102
1-10	97-103
<1	95-105
0.01-0.1	90-110
<0.01	80-120

DG SANCO Guidance document on pesticide residue analytical methods (EU, 2010a)

Where available the active content can be determined in the formulation using a CIPAC method. When a CIPAC method has been validated for the active substance in the same formulation type then full validation data are not required. In such cases only specificity data are required.

For substances of concern and relevant impurities, the same requirements are applicable as for the active substance with additional requirements to confirm the identity of the impurity. If the method used to determine the substance of concern or relevant impurity is not regarded as highly specific then confirmation of the result using a fully validated confirmatory method of analysis is required. See footnote 3 in Chapter II Section 2.11.

For further information on procedures for confirmation of identity see Chapter II Section 5.2.

5.2. In so far as not covered by Annex II 5.2 and 5.3, analytical methods for monitoring purposes (ADS)

including recovery rates and the limits of determination of relevant components of the biocidal product and/or residues thereof, where relevant in or on the following:

Residue definition
Generally, it has to be confirmed during evaluation, where relevant, which relevant components of the biocidal products should be monitored in addition based on its evaluation of fate and behaviour of the components and the toxicological and ecotoxicological potential.

Components of the biocidal product classified as toxic or very toxic are considered to be the toxicologically relevant components (see Chapter II Section 2.11). They must be analysed for monitoring purposes if human exposure cannot be excluded. Validation of the analytical methods employed must be performed.

Limit of quantification
The LOQ should correspond to the limits for the active substance in Chapter II Section 5.2.4.

Components of the biocidal product classified as dangerous for the environment are considered to be the ecotoxicologically relevant components (see Chapter II Section 2.11). They must be analysed for monitoring purposes if environmental exposure cannot be excluded. Validation of the analytical methods employed must be performed.

Limit of quantification
The LOQ should correspond to the limits for the active substance in Chapter II Section 5.2.

5.2.1. Soil (ADS)

Please follow guidance in Chapter II Section 5.2.1.

5.2.2. Air (ADS)

Please follow guidance in Chapter II Section 5.2.2.

5.2.3. Water (including drinking water) and sediment (ADS)

Please follow guidance in Chapter II Section 5.2.3.

5.2.4. Animal and human body fluids and tissues (ADS)

Please follow guidance in Chapter II Section 5.2.4.

5.3. Analytical methods for monitoring purposes including recovery rates and the limit of quantification and detection for the active substance, and for residues thereof, in/on food of plant and animal origin or feeding stuffs and other products where relevant (ADS)

(not necessary if neither the active substance or the material treated with it come into contact with food producing animals, food of plant and animal origin or feeding stuffs)

The requirements for the active substance itself are given in Chapter II Section 5.3. Analytical methods are required for all active substances in a biocidal product.

The quantification of residues of non-active ingredients is required for substances with toxicological concern and for residue levels exceeding 0.01 mg/kg.

Please follow guidance in Chapter II Section 5.3.

6. Effectiveness against target organisms

Please read the introduction in Chapter II Section 6.

The efficacy assessment of a biocidal product is based on substantiating the efficacy claims made for a product. The assessment is made on the product in its normal conditions of use.

All requirements regarding efficacy outlined below apply equally also for the simplified authorisation procedure (Article 20(1)(b) of the BPR).

6.1. Function, e.g. fungicide, rodenticide, insecticide, bactericide and mode of control e.g. attracting, killing, inhibiting

Provide information on the function of the biocidal product.

6.2. Representative organism(s) to be controlled and products, organisms or objects to be protected

For an organism to be controlled provide both the common name and the scientific name when possible and also the sex, strain and stadia where relevant and appropriate. Where complexes of organisms are involved, generic names that are representative of the diversity of the complex must be indicated. Where human and/or animal pathogens are involved, the specific names must be provided.

Indicate in which parts of EU the organisms to be controlled exist.

6.3. Effects on representative target organisms.

The effects on the target organisms required for the claimed efficacy should be described and specified if possible for each use and method of application if these have different effects.

The dependence of the effect on the concentration of the active substance should be indicated.

The possible existence of a threshold concentration for the desired effect should be stated. This is the case if the dependence between the desired effect and the concentration of the active substance is not found (or is much weaker) below a certain concentration (the threshold concentration).

6.4. Likely concentration at which the active substance will be used

The likely use concentrations in the target should be stated for each use and method of application. Indicate if the use concentrations should be different in different parts of EU.

Justification for the selection of the use concentrations should be provided. The likely use concentration should ideally be the minimum effective concentration under real conditions for the respective service life, taking into account all relevant parameters that impact on efficacy.

6.5. Mode of action (including time delay)

The mode of action in terms, where relevant, of the biological, biochemical and physiological mechanisms and biochemical pathways involved should be stated. Information on time delay should be included, where applicable. The information on time does not need to be provided e.g. for products that take some time to manifest their effect such as insect growth regulators. Where available, the results of experimental studies must be reported.

Where it is known that in order to exert its intended effect the active substance must be converted into a metabolite or degradation product following application or use of a preparation containing it, justification should be submitted for why this metabolite or degradation product is not considered to be the active substance. In addition, available information relating to the formation of reactive metabolites or reaction products must be provided. This information must include:

- The chemical name, empirical and structural formula, molecular mass, and CAS and EC (EINECS, ELINCS or No Longer Polymers list) numbers if available;
- The processes, mechanisms and reactions involved;
- Kinetic and other data concerning the rate of conversion and if known the rate limiting step; and
- Environmental and other factors effecting the rate and extent of conversion.

Indicate also if the actual active substance is the result of a combined action of different products (i.e. when such a combination is necessary to achieve the intended effect).

6.6. The proposed label claims for the product and, where label claims are made, for treated articles

The term “label claims” should include all claims made for the efficacy of the product, such as those on advertising material or accompanying leaflets, as well as those on the product label. A

detailed evaluation of the efficacy data against the label claims should be carried out. The evaluation should include all relevant target species (or representative species), the effects of product usage, the duration and speed of effect, any claims for residual action, together with any other specific claims.

6.7. Efficacy data to support these claims,

including any available standard protocols, laboratory tests or field trials used including performance standards where appropriate and relevant.
The TNsG on product evaluation (EU, 2008c) provides further amplification in this area. Although at the time of writing, detailed product-type-specific guidance is not yet available for all product-types and use patterns, details for those product-types currently outstanding are now in preparation. This product-type-specific guidance intended to replace the appendices of the TNsG may be published as separate documents to the TNsG or its revision, and therefore applicants are advised to check for the availability of the revised TNsG or its individual appendices to come. At the time of writing, Sweden was also investigating the issues around testing of the efficacy of treated articles for different product-types which may affect this Guidance with regard to the label claims for treated articles.

The applicant must demonstrate that the biocidal product or treated article is effective and suitable for its intended use when applied according to its instructions for use. This can be confirmed by provision of data that may include laboratory studies, pilot plant or field test data or other relevant study data, provided that the test conditions are comparable with the purpose applied for and with the environmental characteristics relevant for the intended use.

For field studies conducted outside the territory of the Member State in which the authorisation is being sought, a justification of the relevance of such data must be made. The extent of the information required will vary depending on the product-type and proposed use pattern and upon the similarity of the conditions in the two countries. Justification may include, as relevant and appropriate, information on the harmful organism (e.g. comparison of genera/species and its relevance to the Member State in which authorisation is sought), meteorological parameters (e.g. mean temperatures and rainfall) and location details.

For laboratory studies, practical aspects of designing and performing of these trials for testing the efficacy of preservatives (Main Group II: product-types 6-13) are described in the Guidance on the General principles and practical considerations for testing the efficacy of preservatives (EU, xxx, under consultation).

The test method should measure a response and, as appropriate, an endpoint relevant to the label claims. The method should employ an untreated control and, if possible, a reference product for comparison. The efficacy test reports should contain dose response data for dose rates lower than the recommended rate. However, this may not be always possible for field studies.

Where earlier formulations of the product/treated article or other products/treated articles containing the same active substances are cited as supporting evidence, all relevant formulation details must be provided and the relevance of this evidence to the current formulation must be fully justified.

The tests (and data generated) should be based on sound scientific principles and practices. Compliance with quality standards such as ISO 9000 is highly recommended. More detailed guidance on appropriate test methods is provided in paragraph 52 of Annex VI in the BPR and in the TNsG on Product Evaluation (EU, 2008c). An OECD Guidance Document on use of efficacy methods for treated articles and materials is available (OECD, 2007b). A Guidance document on

use of efficacy methods is being developed by the OECD (Overview of Efficacy testing methods for biocides. Draft 1999).

The following product-type-specific guidance should be followed if applicable:

- For product-types 1 and 2, the European standard efficacy method tests of the CEN for disinfectants and antiseptics (e.g. EN13727 and 13624; several others are in preparation) are highly recommended. An overview of all EN tests for disinfectants can be found in EN14885. Relevant OECD Test Guidelines and guidance are available (e.g. OECD Guidance Document for establishing the efficacy of biocides used in swimming pools and spas (OECD, 2012b), several others are being developed.

- For product-types 3, 4 and 5 the European standard efficacy testing methods of the CEN are highly recommended; several of these are in preparation. An overview of all EN tests for disinfectants can be found in EN14885. Relevant OECD tests are being developed. For product-type 5, standard efficacy testing method is in preparation by COM working group. The scope of the test is the application of biocides during the drinking water production and distribution for public supply.

- A product specific Guidance Document on product-types encompassed within Main Group I (product-types 1-5, Disinfectants) can be found in the TNsG on product evaluation (EU, 2008c), the specific appendix is under revision.

- For product-type 8, the European standard efficacy tests of CEN are highly recommended for wood preservatives. These standards are not suitable to all wood preservatives. Modifications to them or development of new ones may be necessary. See specific guidance in the TNsG on product evaluation (EU, 2008c), the specific appendix is under revision.

- For product-type 10, see specific guidance in the TNsG on product evaluation (EU, 2008c) .

- For product-type 14, EPPO guidelines for efficacy testing are highly recommended (e.g. EPPO guidelines 97, 113, 114, 169 and 198 for rodenticides). Further product specific Guidance document on product-type 14 can be found in the TNsG on product evaluation (EU, 2008c) and a revised appendix to chapter 7 on efficacy of rodenticides (EU, 2009b).

- For product-type 16, EPPO guidelines for efficacy testing are highly recommended (e.g. EPPO guidelines 95 for molluscicides in terrestrial environment).

- For product-type 18, see specific guidance in the TNsG on product evaluation (EU, 2008c) and the revised appendix to chapter 7 on efficacy to insecticides and other arthropods (EU, 2012b).

- For product-type 19, EPPO guidelines 199 and 200 are available for efficacy testing of rodent repellents intended for plant protection. These might be modified for biocidal use. For insect repellents see product specific guidance in the TNsG on product evaluation (EU, 2008c) and the revised appendix to chapter 7 on efficacy to insecticides and other arthropods (EU, 2012b).

- For product-type 21, the standard test protocols of CEPE (1993) and ASTM (1987) for conducting efficacy tests are recommended for antifouling products. The latter is an internationally recognised draft test method. Further product specific Guidance document on product-type 21 can be found in the TNsG on product evaluation (EU, 2008c), the specific appendix is under revision.
- For product-type 22, the specific guidance is under development.
- For treated articles of product-type 1, 2, 4, 7, 9 (10) there is an OECD Guidance Document available (OECD, 2008d).

6.8. Any known limitations on efficacy

Provide possible restrictions or recommendations concerning the use of the product in specific environmental or other conditions. State possible factors that can reduce the efficacy, for instance hot, cold or humid environments or the presence of other substances, in addition to the grounds for these. State if the product cannot be mixed with, for example, other biocidal products or if the use of the product with other biocidal products is recommended.

6.8.1. Information on the occurrence or possible occurrence of the development of resistance and appropriate management strategies

Provide information on the occurrence or possible occurrence of the development of resistance and appropriate management strategies, including also cross-resistance. This information must be submitted even where it is not directly relevant to the uses for which authorisation is sought or to be renewed (e.g. different species of harmful organism), as it may provide an indication of the likelihood of resistance development in the target population.

Where there is evidence or information to suggest that in commercial experimental use the development of resistance is likely, evidence must be generated and submitted as to the sensitivity to the substance on the part of the populations of the harmful organism concerned. In such cases a management strategy designed to minimise the likelihood of resistance or cross-resistance developing in target species must be provided. This should include possible recommendations concerning the avoidance of the continuous use of the product in order to prevent the development of resistant strains and the grounds for these. This is addressed in the TNsG on product evaluation (EU, 2008c).

6.8.2. Observations on undesirable or unintended side effects e.g. on beneficial and other non-target organisms

Provide observations on undesirable or unintended side effects. Provideobservations such as on adverse reaction to fastenings and fittings used in wood following the application of a wood preservative, corrosion risk on sanitary fittings following application of disinfectants, etc. Provide informatioon on effects on beneficial and other non-target organisms, only as far as this is not covered under Chapter II and III Section 9.

Provide information on unnecessary suffering and pain for target vertebrates, where relevant.

6.9. Summary and evaluation

The findings on the effectiveness against target organisms (6.1-6.8.2) are summarised and evaluated.

7. Intended uses and exposure

One copy of the draft product label is required. The product label being defined as the written, printed or graphic matter which is printed on, attached to, or otherwise accompanies the biocide containers or other packaging, and by which the user is informed of the requirements for the safe, humane and efficacious use of the product. The product label should include details relating to its identity including tradename, product registration number, formulation type and name and amount of active substance as well as details of the approval holder and marketing company and their respective contact details. It should include details relating to its intended use, method of application, rate, number and timing of applications, safety information and general directions for use. This information must reflect the information contained within the rest of the product dossier.

7.1. Field(s) of use envisaged for biocidal products and, where appropriate, treated articles

Please follow guidance in Chapter II Section 7.1.

7.2. Product-type

Please follow guidance in Chapter II Section 7.2.

7.3. Detailed description of intended use pattern(s) for biocidal products and, where appropriate, treated articles

Please follow guidance in Chapter II Section 7.3.

7.4. User e.g. industrial, trained professional, professional or general public (non-professional)

Please follow guidance in Chapter II Section 7.4.

7.5. Likely tonnage to be placed on the market per year and where relevant, for different use categories

An estimate of the quantity of the product or treated article, respectively, placed or to be placed on the EU market by the applicant (i.e. imported or produced) per year. The quantities for biocidal use and in which product-types, and where relevant, for the envisaged major use categories within each of the product-types. The quantities for use other than as a biocide should be indicated, if available. In case of the renewal of authorisation, tonnage data should cover the last three years. For new products, not previously marketed, production plans covering the next three years after authorisation should be provided.

7.6. Method of application and a description of this method

The method of application of product in different uses should be explained. If the product is to be diluted, the substance used for dilution and the final concentration of the product as well as the active substance in the solution - as a percentage - must be stated. A description of the application technique (e.g. dipping, spreading, spraying, automatic/manual dosing etc.) should be included. The substances that may have to be added to the solution and their dosages must also be given.

If certain technical device will be used together with product, a description of this device should be provided.

If an apparatus is used to produce the active substance *in situ* and dose it directly, information should be provided on safety measures concerning over and under dosing.

7.7. Application rate and if appropriate, the final concentration of the biocidal product and active substance in a treated article or in the system in which the preparation is to be used, e.g. cooling water, surface water, water used for heating purposes.

The recommended dose of the product and the active substance per object should be stated (e.g. per surface area of the material to be protected or as a concentration in a water system).

For product-type 21, the final concentrations of each biocidal component in the antifouling coating layer of the antifouling product and in addition the thickness of the film should also be given.

7.8. Number and timing of applications, and where relevant, any particular information relating to geographical location or climatic variations including necessary waiting periods, clearance times, withdrawal periods or other precautions to protect human and animal health and the environment

Describe, where relevant, how the applications should differ in different parts of EU.

Indicate the recommended duration of application and possible re-applications including estimated life of the treated article if relevant.

The following product-type-specific guidance should be followed if applicable:

- For disinfectants of Main Group 1, potential information on effects of temperature and humidity on the frequency of application must be supplied where relevant. The contact time needed to provide sufficient efficacy should be stated. For veterinary hygiene products (product-type 3) to be used in animal husbandry and products in product-type 4, the waiting periods and for product-type 4, if applicable, the necessity of rinsing or wiping necessary to prevent the dislodging of unacceptable residues from treated equipment in food or feed products should be given.
- For material preservatives of product-types 6 to 10, instructions on the minimum drying time or time to reach resistance to leaching (fixation) of the product in the material treated has to be described. Information on the effects of e.g. temperature and humidity on drying or fixation has to be given, i.e. when the treated material is dry enough for safe exposure of humans and the environment. Furthermore, when possible, a qualitative or quantitative method should be stated for determining that the proper drying or resistance to leaching has been achieved.
- For product-types 11 and 12, when used in an open system with process water, information on the minimum dilution or treatment time for the active substance in waste water should be given in order to assure a sufficient degree of degradation or dilution before it is released to a water course to protect aquatic organisms from harmful effects.
- For pest control products of Main Group 3 and product-type 20, for products used in e.g. fumigation, clearance times sufficient to protect bystanders etc. should be given.

- For molluscicides (product-type 16) and piscicides (product-type 17), necessary waiting periods should be given to prevent harm or dislodging of unacceptable residues from treated tanks or basins for e.g. the subsequent batch of aquaculture.
- For product-type 21, instructions on the minimum drying time of the coating and information on the effects of for instance, temperature and humidity on drying have to be given, i.e. it should be indicated when the coating is dry enough to be ready for launching and whether the coating should be washed before launching in order to reduce the primary release into the aquatic environment. Furthermore, a method for ensuring that a proper coating has been achieved should be given.
- Furthermore for product-type 21, instructions on how to determine the mean biocide release rate and thereby the timing of the next application of the antifouling coating (i.e. the dry-docking or slipping interval) should be given with details on the effects of mean water temperature, vessel speed, salinity, etc. on the release rate and length of the service period of the coating.

7.9. Proposed instructions for use

7.10. Exposure data in conformity with Annex VI of this Regulation

According to Annex VI on the common principles for the evaluation of dossiers for biocidal products, an exposure assessment needs to be carried out for human and environmental populations for which exposure to a biocidal product occurs or can reasonably be foreseen.

For further guidance on exposure assessment see part B of the BPR technical Guidance (BPR guidance under development).

7.10.1. Information on human exposure associated with production and formulation, proposed/expected uses and disposal

Sufficient information on exposure to the biocidal product likely to occur during the proposed conditions of use must be submitted. The information should include all relevant stages of production and formulation and of use and all possible exposure routes. Actual exposure data and/or calculations using recommended models are acceptable. Test reports of any studies conducted because an exposure of the biocidal product on humans through the particular route is possible must be submitted. An expert judgment is needed to decide if any other studies are required (see Chapter 1.2, point 4). A starting point is assessment of human exposures to biocides, see part B of the BPR technical Guidance (BPR guidance under development).

Please also follow guidance in Chapter II Section 7.6.1.

7.10.2. Information on environmental exposure associated with production and formulation, proposed/expected uses and disposal

Please follow guidance in Chapter II Section 7.6.2.

7.10.3. Information on exposure from treated articles including leaching data (either laboratory studies or model data)

Please follow guidance in Chapter II Section 7.6.4

7.10.4. Information regarding other products that the product is likely to be used together with, in particular the identity of the active substances in these products, if relevant, and the likelihood of any interactions

Possible incompatibility with any products or active substances should be mentioned.

8. Toxicological profile for humans and animals

This chapter describes the information requirements for biocidal products for the assessment of the toxicological profile for humans and animals.

8.1. Skin corrosion or skin irritation

The assessment of this endpoint shall be carried out according to the sequential testing strategy for dermal irritation and corrosion set out in the Appendix to Test Guideline B.4. Acute Toxicity - Dermal Irritation/Corrosion (Annex B.4. to Regulation (EC) No 440/2008).

Testing on the product/mixture does not need to be conducted if

- *there are valid data available on each of the components in the mixture sufficient to allow classification of the mixture according to the rules laid down in Directive 1999/45/EC and Regulation (EC) No 1272/2008 (CLP), and synergistic effects between any of the components are not expected.*

Please follow the guidance in Chapter II Section 8.1.

8.2. Eye irritation

The assessment of this endpoint shall be carried out according to the sequential testing strategy for eye irritation and corrosion as set down in the Appendix to Test Guideline B.5.Acute Toxicity: Eye Irritation/Corrosion (Annex B.5. to Regulation (EC) No 440/2008).

Testing on the product/mixture does not need to be conducted if:

- *there are valid data available on each of the components in the mixture sufficient to allow classification of the mixture according to the rules laid down in Directive 1999/45/EC and Regulation (EC) No 1272/2008 (CLP), and synergistic effects between any of the components are not expected.*

Please follow the guidance in Chapter II Section 8.2.

8.3. Skin sensitisation

The assessment of this endpoint shall comprise the following consecutive steps:

1. *an assessment of the available human, animal and alternative data*
2. *in vivo testing*

The Murine Local Lymph Node Assay (LLNA) including, where appropriate, the reduced variant of the assay, is the first-choice method for in vivo testing. If another skin sensitisation test is used justification shall be provided.

Testing on the product/mixture does not need to be conducted if:

- *there are valid data available on each of the components in the mixture sufficient to allow classification of the mixture according to the rules laid down in Directive 1999/45/EC and Regulation (EC) No 1272/2008 (CLP), and synergistic effects between any of the components are not expected;*
- *the available information indicates that the product should be classified for skin sensitisation or corrosivity; or*
- *the substance is a strong acid (pH < 2.0) or base (pH > 11.5)*

Please follow the guidance in Chapter II Section 8.3.

Any limitation of the additivity method specified in the Guidance on the Application of the CLP Criteria (ECHA, 2012a) in the for sensitisation with regard to addressing sub corrosive concentrations with sensitising potential should also be considered (see also Chapter II Section 8.3).

8.4. Respiratory sensitisation (ADS)

Testing on the product/mixture does not need to be conducted if:

- *there are valid data available on each of the components in the mixture sufficient to allow classification of the mixture according to the rules laid down in Directive 1999/45/EC and Regulation (EC) No 1272/2008 (CLP), and synergistic effects between any of the components are not expected.*

Please follow the guidance in Chapter II Section 8.4.

8.5. Acute toxicity

- *Classification using the tiered approach to classification of mixtures for acute toxicity in Regulation (EC) No 1272/2008 is the default approach*

Testing on the product/mixture does not need to be conducted if:

- *there are valid data available on each of the components in the mixture sufficient to allow classification of the mixture according to the rules laid down in Directive 1999/45/EC and Regulation (EC) No 1272/2008 (CLP), and synergistic effects between any of the components are not expected.*

8.5.1. By oral route

Please follow guidance in Chapter II Section 8.7.1.

8.5.2. By inhalation

Please follow guidance in Chapter II Section 8.7.2.

8.5.3. By dermal route

Please follow guidance in Chapter II Section 8.7.3.

8.5.4. For biocidal products that are intended to be authorised for use with other biocidal products,

the risks to human health, animal health and the environment arising from the use of these product combinations shall be assessed. As an alternative to acute toxicity studies, calculations can be used. In some cases, for example where there are no valid data available of the kind set out in column 3, this may require a limited number of acute toxicity studies to be carried out using combinations of the products

Testing on the mixture of products does not need to be conducted if:

- *there are valid data available on each of the components in the mixture sufficient to allow classification of the mixture according to the rules laid down in Directive 1999/45/EC and Regulation (EC) No 1272/2008 (CLP), and synergistic effects between any of the components are not expected.*

8.6. Information on dermal absorption

Information on dermal absorption when exposure occurs to the biocidal product. The assessment of this endpoint shall proceed using a tiered approach

It is not always mandatory to submit experimental data. If such data are not available, as a first step default values (depending on physicochemical properties of the active substance) can be used (additional guidance provided in Part B of Hazard Identification within the Toxicokinetics chapter (BPR guidance under development)). The OECD Guidance Document on Percutaneous absorption/penetration (OECD, 2004a) and the EFSA Guidance Document on Dermal Absorption (EFSA, 2012) should be followed where applicable for the estimation of dermal absorption both for the biocidal product and the active substance (Chapter II Section 8.8).

The following Test Guidelines are available for the conduct of skin absorption studies:

- EC method B.45 Skin Absorption: *In Vitro* Method.
- OECD Test Guideline 428: Skin Absorption: *In Vitro* Method.
- EC method B.44 Skin Absorption: *In Vivo* Method.
- OECD Test Guideline 427: Skin Absorption: *In Vivo* Method.

If testing to assess the likely magnitude and rate of dermal bioavailability is necessary the OECD Test Guideline 428 for *in vitro* skin absorption should be considered first.

Dermal absorption can be estimated on the basis of existing information that comes from other sources. Mostly, this will be extrapolation of experimental data obtained with a similar formulation, but in this case strict and transparent rules should be followed as to when another formulation or product can be considered similar. Expert judgment will always be needed in these cases as well as justification of less frequently used approaches such as the application of QSARs or a comparison of the results obtained in oral and dermal toxicity studies.

Before new studies are commenced, it should be checked whether the intended use is safe when the appropriate default value is applied. If no experimental data are available, studies with similar formulations should be looked for or further information used that may give at least a rough estimate. If valid studies with the same formulation for which authorisation is to be granted have been performed, their results should be used with a preference to an *in vitro* study on human skin.

Dermal absorption can be measured *in vitro* and/or *in vivo*. If valid studies with the formulation to be regulated are available, their results should be directly used for risk assessment. However, deviations from OECD TG 427 and OECD TG 428 require justification including an assessment of the impact of the deviation. Acceptable studies should be in full compliance with OECD test guidelines 427 (*in vivo*) or 428 (*in vitro*) or at least similar to them in all main aspects, based on expert judgement. The applicant should ensure to provide the necessary relevant information in the study report, e.g. regarding the use of tape stripping. It must be acknowledged that both guidelines leave a certain degree of freedom to modify the study design. Although it is widely accepted that the so-called "triple pack", i.e., a combination of *in vivo* (rat) and *in vitro* (comparison of permeability through human and rat skin) data will provide the most reliable prediction of dermal absorption in man, *in vitro* studies on human skin are considered sufficiently predictive and conservative. Therefore, *in vitro* results obtained on human skin should be normally used for the risk assessment and a complete "triple pack" including testing in living animals will not be required. However, available triple pack data may be used for refinement of the assessment. Likewise, *in vivo* studies on rats or in vitro studies on rat skin as "stand alone" information may also be used but it should be acknowledged that, in the vast majority of cases will result in clear overestimation of dermal absorption in humans.

Other types of studies (e.g., in human volunteers) could be taken into consideration in exceptional cases but in general their use is not recommended.

8.7. Available toxicological data relating to:

– non-active substance(s) (i.e. substance(s) of concern), or

– a mixture that a substance(s) of concern is a component of

If insufficient data are available for a non-active substance(s) and cannot be inferred through read-across or other accepted non-testing approaches, targeted test(s) described in Annex II, shall be carried out for the […] substance(s) of concern or a mixture that a substance(s) of concern is a component of.

Testing on the product/mixture does not need to be conducted if:

- *there are valid data available on each of the components in the mixture sufficient to allow classification of the mixture according to the rules laid down in Directive 1999/45/EC and Regulation (EC) No 1272/2008 (CLP), and synergistic effects between any of the components are not expected.*

8.8. Food and feedingstuffs studies (ADS)

8.8.1. If residues of the biocidal product remain on feedingstuffs for a significant period of time, then feeding and metabolism studies in livestock shall be required to permit evaluation of residues in food of animal origin (ADS)

Please follow guidance in Chapter II Section 8.16.

8.9. Effects of industrial processing and/or domestic preparation on the nature and magnitude of residues of the biocidal product (ADS)

The objective of these studies is to establish whether or not breakdown or reaction products arise from residues in the raw products during processing which may require a separate risk assessment.

Depending upon the level and chemical nature of the residue in the raw commodity, a set of representative hydrolysis situations (simulating the relevant processing operations) should be investigated, where appropriate. The effects of process other than hydrolysis may also have to be investigated, where the properties of the active substance or metabolites indicate that toxicologically significant degradation products may occur as a result of these processes. The studies are normally conducted with a radio-labelled form of the active substance.

Please follow guidance in Chapter II Section 8.16.

8.10. Other test(s) related to the exposure to humans (ADS)

Suitable test(s) and a reasoned case will be required for the biocidal product.

In addition, for certain biocides which are applied directly or around livestock (including horses) residue studies might be needed.

Please follow guidance in Chapter II Section 8.16.

9. Ecotoxicological studies

9.1. Information relating to the ecotoxicity of the biocidal product which is sufficient to enable a decision to be made concerning the classification of the product is required.

- *Where there are valid data available on each of the components in the mixture and synergistic effects between any of the components are not expected, classification of the mixture can be made according to the rules laid down in Directive 1999/45/EC, Regulation (EC) No 1907/2006 (REACH) and Regulation (EC) No 1272/2008 (CLP).*
- *Where valid data on the components are not available or where synergistic effects may be expected then testing of components and/or the biocidal product itself may be necessary.*

Synergistic effects are defined as an interaction between two or more components of the product leading to an effect of the mixture which is greater than that expected by concentration addition by a factor of 5.

9.2. Further Ecotoxicological studies

Further studies chosen from among the endpoints referred to in section 9 of Annex II for relevant components of the biocidal product or the biocidal product itself may be required if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product.

For the determination of the relevant components, see Guidance for mixture toxicity assessment (under development).

9.3. Effects on any other specific, non-target organisms (flora and fauna) believed to be at risk (ADS)

Such testing may be required if tests on other non-target organisms are needed on the basis of intended uses and results from the other tests in Chapter II (data set for the active substance) or a preliminary risk assessment. For instance, tests on sediment dwelling organisms, aquatic plant

growth (including macro-algae), accumulation and elimination in shellfish or tests on marine macro-algae or other additional tests on estuarine and marine organisms may be needed.

The decision on the need of such further studies should be decided on a case-by-case basis after consulting with the competent authority.

Data for the assessment of hazards to wild mammals are derived from the mammalian toxicological assessment.

9.4. If the biocidal product is in the form of bait or granules the following studies may be required:

9.4.1. Supervised trials to assess risks to non-target organisms under field conditions

This endpoint concerns non-target organisms for which the use pattern of the biocidal product may lead to direct or indirect exposure, which, in combination with the mode of action and critical effects of the substance, raise concern. Examples are honey bees or other arthropods which may be exposed to insecticides under field conditions, or birds and mammals which may be exposed to rodenticides either by direct consumption of the product or through their diet via preying or scavenging on exposed animals. For honeybees, Guidance is currently being drafted. See also Chapter II and the product-type-specific guidance in Chapter V.

Further Guidance:

- Guidance on information requirements and chemical safety assessment Chapter R7b: R.7.11 Effects on terrestrial organisms (ECHA, 2012c);
- Guidance on risk assessment for birds and mammals (EFSA, 2009a).

9.4.2. Studies on acceptance by ingestion of the biocidal product by any non-target organisms thought to be at risk

In order to assess risks to predators or scavengers, residue data in target organisms concerning the active substance and including toxicologically relevant metabolites would be needed. For birds a study on avoidance should be made according to the OECD draft Guidance document on avoidance of testing on birds (OECD, 2011).

9.5. Secondary ecological effect e.g. when a large proportion of a specific habitat type is treated (ADS)

As a refinement higher tier field studies (soil and/or water-sediment compartment) may be required to identify secondary ecological effects when a habitat such as a water body, wetland, forest or field is treated. A habitat may vary significantly in size as well as biological complexity, and the requirement for a field study, as well as its scope, must therefore be tailored to the type of habitat to be treated, and how it is treated. The judgement of whether a large proportion is treated should concern not only the whole habitat area but importantly potential exposure to important physical and ecological components or zones of the habitat/ecosystem such as keystone species, food components or zones for spawning, nesting or foraging. The assessment may concern a range of different trophic levels and species from micro-organisms to top predators.

Ecological effects of biocides are varied and are often inter-related with other effects. Major types of effects are listed below and will vary depending on the organism, community or habitat under

investigation and the type of biocide. Different biocides have markedly different effects on aquatic/soil life which makes generalisation very difficult. Effects expressed on the level of individuals may ultimately compromise the long-term viability and performance of species populations and also affect community or ecosystem structure and function.

- Death of the organism
- Cancers, tumours and lesions on fish and animals
- Reproductive inhibition or failure
- Suppression of immune system
- Disruption of endocrine (hormonal) system
- Cellular and DNA damage
- Teratogenic effects (physical deformities such as hooked beaks on birds)
- Poor fish health marked by low red to white blood cell ratio, excessive slime on fish scales and gills, etc.
- Other physiological effects such as egg shell thinning
- Intergenerational effects (effects are not apparent until subsequent generations of the organism). Can include for example changes in growth and development or impairment of reproductive capacity in individuals, or genetic drift or change in sex ratio in the population
- Altered species succession
- Altered community or ecosystem structure
- Altered energy transfer and trophic state
- Tolerance development on a species or community level
- Decline in biodiversity, imparied ecological functions and services

These effects are not necessarily caused solely by exposure to biocides, pesticides or other organic contaminants, but may be associated with a combination of environmental stressors such as eutrophication, alien species and pathogens.

Aim of the test
The test should provide sufficient data to evaluate possible effects at species, population or community and ecosystem level.

Test conditions
Studies must be carried out in systems representative to habitats to which the product is applied. Important aspects to consider are e.g. the use of reference areas, replicates history of the (treated and non-treated) areas, climatic conditions, timing, duration of exposure, frequency, dosage and concentration distribution in time and location.

Test guideline
There are no internationally agreed standard protocols for field studies, only recommendations mainly developed within the Plant Protection framework, which may be helpful. In contrast to laboratory tests rigid protocols are not desirable for field studies. The trial should rather be designed individually addressing the problems that have been identified. Consult the list below for recommedations regarding field studies:

- Ecological effects of pesticide use in the Netherlands. Modeled and observed effects in the field ditch; RIVM report 500002003 (de Zwart, 2003)

- Guidelines for ecological impact assessment in the United Kingdom (IEEM, 2006)Exposure and ecological effects of toxic mixtures at field-relevant concentrations. Model validation

and integration of the SSEO programme; RIVM Report 860706002/2007 (Eijsackers, et al., 2007)

- Guidance for summarizing and evaluating aquatic micro- and mesocosm studies; RIVM Report 601506009/2008 (de Jong, Brock, Foekema, & Leeuwangh, 2008).
- Ecological effects of pesticides (FAO, 1996)
- Ecological Monitoring Methods. (Grant & Tingle, 2002)

10. Environmental fate and behaviour

The test requirements below are applicable only to the relevant components of the biocidal product.

Product-type-specific guidance on this issue is given in Chapter V.

10.1. Foreseeable routes of entry into the environment on the basis of the use envisaged

Information on how the active substance or a substance of concern due to handling it or from a waste water treatment plant etc. to which compartment of the environment (soil, sediment, water, air) can be released into the environment, and an estimation on how large the amounts released are.

Sources of environmental exposure: for example production, distribution, storage, mixing and loading, uses and disposal or recovery should be described. The measured or estimated extent of release: frequency and intensity (e.g. dose and duration) should be indicated. The descriptions should cover the most significant routes of exposure.

Define aquatic recipients in detail: for instance surface water, groundwater, estuaries or marine environment. Assess possible ways of transformation and distribution.

Information on representative measured concentrations or monitoring data, for example, in wastewater or in the environment or on concentrations based on model calculations, and which can be used as predicted environmental concentrations in the relevant environmental compartments.

10.2. Further studies on fate and behaviour in the environment (ADS)

Further studies chosen from among the endpoints referred to in Section 10 of Annex II for relevant components of the biocidal product or the biocidal product itself may be required.

For products that are used outside, with direct emission to soil, water or surfaces, the components in the product may influence the fate and behaviour (and ecotoxicity) of the active substance. Data are required unless it is scientifically justified that the fate of the components in the product is covered by the data provided for the active substance and other identified substances of concern.

10.3. Leaching behaviour (ADS)

For treated articles, please refer to Chapter II Section 7.6.4.

The type of leaching test to be provided is highly depending on the product type and the specific use of the biocidal product, respectively. For many product types, no harmonised leaching test guidelines are available yet. However, for product type 8 the following guidelines were agreed upon during the discussion under the review programme. Therefore they may be a starting point for other product types as well.

Use class 3, laboratory tests:

- Series on Testing and Assessment Number 107 – Preservative-treated wood to the environment: For wood held in storage after treatment and for wooden commodities that are not in contact with ground; ENV/JM/MONO 2009(12) (OECD, 2009b).
- CEN/TS 15119-1: Durability of wood and wood-based products — Determination of emissions from preservative treated wood to the environment — Part 1: Wood held in the storage yard after treatment and wooden commodities exposed in use Class 3 (not covered, not in contact with the ground) — Laboratory method.

Use class 3, semi-field test:

- Nordtest method NT Build 509 Leaching of active ingredients from preservative-treated timber – semi-field testing.

Use classes 4 & 5, laboratory tests:

- OECD Test Guideline 313 'Estimation of Emissions from Preservatives – Treated Wood to the Environment: Laboratory Method for Wooden Commodities that are not covered and are in Contact with Freshwater or Seawater'.
- CEN/TS 15119-2: Durability of wood and wood-based products — Determination of emissions from preservative treated wood to the environment — Part 2: Wooden commodities exposed in use class 4 or 5 (in contact with the ground, fresh water or sea water) — Laboratory method.

Please contact the evaluating MSCA before conducting new leaching tests to clarify the conditions under which a test should be conducted.

10.4. Testing for distribution and dissipation in the following: (ADS)

In principle, no further distribution and dissipation studies with the product in soil are required and information on distribution and degradation for the active substance, transformation products and substances of concern present in the biocidal product is sufficient. However, if there are indications that other components in the product influence distribution and degradation characteristics, this may trigger additional studies. The same test guidelines described for the active substance tested with the product should be used.

10.4.1. Soil (ADS)

See guidance in Chapter II Section 10.2.

10.4.2. Water and sediment (ADS)

See guidance in Chapter II Section 10.1.

10.4.3. Air (ADS)

See guidance in Chapter II Section 10.3.

10.5. If the biocidal product is to be sprayed near to surface waters then an overspray study may be required to assess risks to aquatic organisms or plants under field conditions (ADS)

The aquatic risk from overspray exposure needs to be assessed with either field studies or mathematical models. So far, there is no harmonised approach available for the risk assessment of biocides. FOCUS 'Surface Water' is the recommended model application for the assessment of plant protection products (EU, 2012c); however, to suit for biocidal uses, e.g. the input parameters would need to be adapted. Furthermore, it would be necessary to clarify which scenarios are representative for the emission of biocidal products and whether to use the outcome of FOCUS models for surface water and/or sediment assessment.

Further Guidance:

- DG SANCO Guidance Document on Aquatic Ecotoxicology, a detailed working document, (EU, 2002b)

10.6. If the biocidal product is to be sprayed outside or if potential for large scale formation of dust is given then data on overspray behaviour may be required to assess risks to bees and non-target arthropods under field conditions (ADS)

Currently, Guidance is under development.

11. Measures to be adopted to protect humans, animals and the environment

11.1. Recommended methods and precautions concerning handling, use, storage, disposal, transport or fire

See guidance in Chapter II Section 11.1.

11.2. Identity of relevant combustion products in cases of fire

See guidance in Chapter II Section 11.2.

11.3. Specific treatment in case of an accident, e.g. first-aid measures, antidotes, medical treatment if available; emergency measures to protect the environment

See guidance in Chapter II Section 11.3.

11.4. Possibility of destruction or decontamination following release in or on the following:

11.4.1. Air

See guidance in Chapter II Section 11.4.

11.4.2. Water, including drinking water

See guidance in Chapter II Section 11.4.

11.4.3. Soil

See guidance in Chapter II Section 11.4.

11.5. Procedures for waste management of the biocidal product and its packaging for industrial use, use by trained professionals, professional users and non-professional users (e.g. possibility of reuse or recycling, neutralisation, conditions for controlled discharge, and incineration)

Provide information necessary for safe disposal. If preliminary treatment of the waste is necessary, information about this must also be provided. If any waste generated is classified as hazardous waste (e.g. according to Commission Decision 2000/532/EC), this has to be mentioned separately and appropriate handling according to the related legislation has to be indicated. The possibility of recovery or recycling should be indicated for both normal uses of the substance and quantities involved in spills.

A chemical or other disposal method for the product should be indicated. Furthermore, information on disposal methods for the waste generated when using the product should also be provided (e.g. precipitates generated, instruments for spreading, residues treated with the product).

Information must be provided on how the package is to be emptied and cleaned and on the recycling or disposal method for empty packages.

Recycling or disposal methods for the waste generated from a treated product, and in the processing of the treated product (e.g. shavings, cuttings or other waste from the treated product) and for treated products no longer in use (e.g. impregnated wood) should be described, if applicable.

Recycling or disposal methods for the waste generated from a treated material (e.g. for chips from metal-cutting where the product is used), and in the processing of the possible treated material (e.g. waste from treated paper pulp or porous sand strata for product-type 12) and for treated material or treated process water or metal working fluid no longer used should be provided, if applicable.

The Guidance provided for the corresponding data requirement for the active substance applies also here.

When the product is applied to a system with water which is to be released into surface water with or without pre-treatment, as may be for product-type 11 and 12, information on the necessary waste water treatment methods and times and/or the on minimum dilution for the active substance in waste water should be provided (in order to assure a sufficient degree of degradation or dilution before being released into a water course to protect aquatic organisms from harmful effects).

11.6. Procedures for cleaning application equipment where relevant

The procedures should be such that the likelihood of accidental contamination of water or its sediments is minimised.

11.7. Specify any repellents or poison control measures included in the product that are present to prevent action against non-target organisms

If mitigation measures are proposed to prevent action against non-target organisms then accuracy of these mitigation measures must be proved resulting in a safe use.

12. Classification, labelling and packaging

As established in point (b) of Article 20(1), proposals including justification for the hazard and precautionary statements in accordance with the provisions set in Directive 1999/45/EC and Regulation (EC) No 1272/2008 must be submitted.

Example labels, instructions for use and safety data sheets shall be provided.

An applicant for authorisation of a biocidal product must propose classification, labelling and packaging which complies with the CLP Regulation or – until 1 June 2015 – the Dangerous Preparations Directive.

Transition to CLP – issues to consider
The CLP Regulation entered into force on 20 January 2009. Article 61 of CLP provides transitional provisions which affect also the classification and labelling of biocidal products. During the transitional period, the following directives are applicable to biocidal products and their components:

- Directive 67/548/EEC (Dangerous Substances Directive, DSD)
- Directive 1999/45/EC (Dangerous Preparations Directive, DPD)

From 1 June 2015, CLP will replace DSD and DPD. Until that time, the timetables are as follows (Article 61 of CLP):

From 1 December 2010 to 1 June 2015:
Substances must be classified in accordance with both DSD and CLP in order to allow these classifications to be used in the classifications of mixtures. Classification and labelling information in accordance with both systems must be included in SDS. Labelling and packaging must be in accordance with CLP Regulation.

Mixtures classification and labelling must be done in accordance with DPD. However, mixtures may alternatively be classified, labelled and packaged in accordance with CLP. In that case mixtures may not be labelled and packaged according to DPD. When a mixture is classified, labelled and packaged according to CLP, classification and labelling information according to both systems must be provided in SDS.

From 1 June 2015:
DSD and DPD are repealed from 1 June 2015 and classification according to these directives is not allowed. Only CLP criteria must be applied for classification, labelling and packaging of both substances and mixtures.

However, mixtures classified, labelled and packaged in accordance with DPD and already placed on the market before 1 June 2015, are not required to be relabelled and repackaged in accordance with CLP until 1 June 2017.

Although applicants cannot be required to propose labelling for mixtures complying with the CLP Regulation before 1 June 2015, it is recommended to consider doing so on a voluntary basis, where possible while any authorisation valid beyond 1 June 2015 would have to be amended as of that date with regard to the hazard and precautionary statements included in the authorised summary of the biocidal products characteristics (SPC), in order to reflect the rules of the CLP Regulation.

In accordance with Articles 6(4) and 7(3) of the DPD and Article 15 of the CLP Regulation, when manufacturers, importers or downstream users placing a substance or mixture on the market may have to re-classify it at any time in light of new scientific or technical information, or following a change in composition.

In accordance with Article 4 of CLP, the responsibility for classification lies with the manufacturer, importer or downstream user who places a (substance or) mixture, such as biocidal products, on the market. CLP requires self-classification[11] by industry of the (substances or) mixtures they supply. Mixtures must always be self-classified according to the criteria and rules provided in the CLP text. All biocidal active substances are normally subject to harmonised C&L for all endpoints, however this is not the case for non-active ingredients (please consult Annex VI of CLP (Article 36(2) of CLP)).

Hazard classification is a process involving identification of the physical, health and environmental hazards of a substance or a mixture, followed by comparison of those hazards (including degree of hazard) with defined criteria in order to arrive at a classification of the (substance or) mixture.

The need for classification of biocidal products must be considered based on relevant available information. According to DPD respectively CLP, for mixtures (such as biocidal products), classification for physical hazards should normally be based on the results of tests carried out on the mixtures themselves. When considering health and environmental hazards, the classification should preferably be based on available information (including test data) on the mixture itself, except when classifying for e.g. CMR effects or for the evaluation in relation to the bioaccumulation and degradation properties within the 'hazardous to the aquatic environment' hazard class referred to in Sections 4.1.2.8 and 4.1.2.9 of Annex I to CLP. In these cases classification of the mixtures should be based on the information on the substances. If no *in vivo* test data are available on a mixture, such data should normally not be generated; rather, all available information on the ingredients of the mixture should be used to derive a classification. Only when the manufacturer, importer or downstream user has exhausted all other means of generating information, new tests may be performed.The background information should be clearly presented in the relevant sections of the dossier (see Chapter III, Sections 4, 8, 9 and 10).

The Guidance documents on the application of Regulation (EC) No 1272/2008 (ECHA, 2012a) provide a detailed guide on the application of CLP criteria. These documents should be used in the light of BPR requirements.

[11] For the purposes of this Guidance self-classification is defined as the decision on a particular hazard C&L of a (substance or) mixture is taken by the manufacturer, importer or downstream user of that (substance or) mixture, or, where applicable, by those producers of articles who have the obligation to classify.

12.1. Hazard classification

A (substance or a) mixture fulfilling the criteria relating to physical hazards, health hazards or environmental hazards, laid down in Parts 2 to 5 of Annex I to CLP respectively DPD is hazardous and must be classified in relation to the respective hazard classes provided for in that Annex respectively DPD.

For further information on the classification criteria refer to Guidance on the application of the CLP criteria, Part 1 (ECHA, 2012a).

12.2. Hazard pictogram

A (substance or) mixture classified as hazardous must bear a label which includes relevant hazard pictograms in accordance with Article 19 of CLP, where applicable.

For further information on the hazard pictograms refer to **Chapter 4.3 Hazard Pictograms** in the Guidance document on Labelling and Packaging in accordance with Regulation (EC) No 1272/2008 (ECHA, 2011b).

Pictograms can be downloaded free of charge from the webpage:
http://www.unece.org/trans/danger/publi/ghs/pictograms.html

12.3. Signal word

A (substance or) mixture classified as hazardous must bear a label which includes a relevant signal word in accordance with Article 20 of CLP, where applicable.

For further information on the signal word please refer to **Chapter 4.4 Signal Words** in the Guidance document on Labelling and Packaging in accordance with Regulation (EC) No 1272/2008 (ECHA, 2011b).

12.4. Hazard statements

A (substance or) mixture classified as hazardous must bear a label which includes the relevant hazard statements in accordance with Article 21 of CLP, where applicable.

For further information on the hazard statements please refer to **Chapter 4.5 Hazard statement** in the Guidance document on Labelling and Packaging in accordance with Regulation (EC) No 1272/2008 (ECHA, 2011b).

A (substance or) mixture classified as hazardous must bear a label which includes relevant supplemental hazard information in accordance with Article 25 of CLP, where applicable.

For further information on the supplemental hazard information please refer to **Chapter 4.8 Supplemental labelling information** in the Guidance document on Labelling and Packaging in accordance with Regulation (EC) No 1272/2008 (ECHA, 2011b).

12.5. Precautionary statements including prevention, response, storage and disposal

A mixture classified as hazardous must bear a label which includes relevant precautionary statements in accordance with Article 22 of CLP, where applicable.

Annex I and Annex IV of the CLP outline the types of precautionary statements.

For further information on the precautionary statements please refer to **Chapter 4.6 Precautionary Statements** in the Guidance document on Labelling and Packaging in accordance with Regulation (EC) No 1272/2008 (ECHA, 2011b).

12.6. Proposals for safety data sheets should be provided, where appropriate

Safety data sheets for active substances and biocidal products should be prepared and made available in accordance with Article 31 of Regulation (EC) No 1907/2006, where applicable. They must be included in the application for product authorisation, where appropriate.

Further Guidance:

- ECHA Guidance on the compilation of safety data sheets (ECHA, 2011c), under revision

12.7. Packaging (type, materials, size, etc.), compatibility of the product with proposed packaging materials to be included

A justification for the packaging (type, materials, size etc.) and the compatibility of the product with proposed packaging materials must be provided. Packaging must be in compliance with Article 35 of CLP resp. DPD.

Further Guidance:

- ECHA Guidance on the Application of the CLP Criteria (ECHA, 2012a)

13. Evaluation and Summary

The key information identified from the endpoints in each subsection (2-12) is summarised, evaluated and a draft risk assessment is performed.

The summary and evaluation must be provided in separate assessment documents attached to the IUCLID file (the templates will be available on the ECHA website).

The Decision on technical equivalence if relevant should be also provided.

IV. TESTING STRATEGIES

4.1. Testing strategy for abiotic degradation

Information on abiotic degradation in water and air is part of the core data set as they are valuable parameters to be considered, e.g. for further laboratory studies and identification of metabolite formation.

For the aquatic compartment, the results from the initial abiotic degradation tests on hydrolysis (Chapter II Section 10.1.1.1.a) might be taken into account in the exposure assessment if not already covered by results on biodegradation. Degradation via phototransformation (Chapter II Section 10.1.1.1.b) is in most cases not to be taken into account in the exposure assessment due to the high turbidity of most water bodies. Only in case of very clear water (e.g. in open sea), phototransformation might be considered in the exposure assessment.

Metabolites formed in the aquatic compartment as major metabolites (see definition in Chapter I Section 1.6) should be included in a conservative first tier exposure assessment. Where metabolites are formed in significant levels they should also be included for consideration in the environmental risk assessment to address the risk in those water bodies where photolysis may be an important fate pathway.

For the atmosphere, estimation of the phototransformation in air (Chapter II Section 10.3.1) is required for active substances of all product-types as a part of their preliminary risk assessment. Additional data on abiotic degradation in the atmosphere (Chapter II Section 10.3.2 Fate and behaviour in air, further studies) are initially required only for active substances which are to be used as fumigants. This study may also be necessary for any other active substance if the preliminary risk assessment shows risk for the atmosphere.

4.2. Testing strategy on biodegradation of biocidal active substances

4.2.1. Aim

A strategy on biodegradation and application in risk assessment for organic compounds has been developed which:

- delivers degradation rate constants for use in the risk assessment,
- provides information on (relevant) metabolites formed,
- makes use of all available data,
- avoids unnecessary (and expensive) testing as much as possible and
- is based on accepted guidance as much as possible.

The resulting biodegradation testing strategy is represented in Figure 5.

4.2.2. (Eco)Toxicity

Many biocides have an anti-bacterial activity. This may pose a problem for biodegradability testing of biocides. Biocides which are toxic to the inoculum may give false negative test results, which may lead to requirements for further tests and/or will influence the outcome of risk assessments. Therefore it is recommended to test the toxicity to bacteria before commencing with biodegradation studies, and to relate the outcome of the toxicity test to the circumstances (e.g. substance concentration) prescribed for the biodegradation studies foreseen. Thus the most

appropriate biodegradation test can be selected. The inhibition of the respiration of activated sludge can be tested using EC method C.11 (Biodegradation: Activated Sludge Respiration Inhibition)or the corresponding OECD Test Guideline 209 (Activated Sludge, Respiration Inhibition Test). It must be noted however, that this test is rather insensitive due to the high biomass content used. Notes on the evaluation of chemicals which may be toxic in ready biodegradability tests are provided in Annex IV to EC method C.4. A-F (Determination of 'Ready' Biodegradability) or the corresponding OECD Test Guideline 301 (Ready Biodegradability) A-F. That annex suggests testing substance concentrations at less than 1/10 of the EC_{50}. The 'closed bottle' test method EC C.4 E (corresponding to OECD Test Guideline 301 E) is normally performed with substance concentrations down to 2 mg/l. For lower concentrations, the use of ^{14}C-labelled material will generally be required. Especially for biocides which may be toxic for bacteria at concentrations used in the standard ready or inherent biodegradability tests, it is advised to enter directly into simulation tests for the relevant compartment, using environmentally relevant concentrations of radiolabelled material.

4.2.3. Temperature

The results of (laboratory) biodegradation studies should be calculated to reflect an average EU ambient temperature of 12 °C:

$$DegT_{50}\ (12\ ^{\circ}C) = DegT_{50}\ (t) \times e^{(0.08 \times (T-12))}$$

Note: Please make sure the right input parameter is used in any model calculations (e.g. EUSES, MAMPEC, PEARL, PELMO) as the Q10 factor is currently not harmonised in all regulatory contexts.

4.2.4. Screening tests

The screening tests have a long history, are standardised and therefore have been incorporated in many chemical substance legislations. There are, however, a number of drawbacks attached to the current EC methods and the corresponding OECD ready and inherent biodegradability tests. In general the current tests have been designed to categorise substances in readily vs. not-readily or inherently vs. not-inherently biodegradable. They do not deliver rate constants for primary degradation of parent compounds. Default rate-constants have been attached to these tests in order to be able to use them for risk assessment. For biocides an important drawback may be that they require rather high substance concentrations (2-400 mg/l), which may give toxicity problems. Furthermore, such high substrate concentrations are generally not in line with the circumstances in which biodegradation takes place in reality. Degradation kinetics at high substrate concentrations may differ from those at lower concentrations.

The screening tests do not provide information on the formation of metabolites (other than mineralisation products). Substances which are either readily biodegradable or inherently biodegradable (according to the above criteria) can be considered to have such a high mineralisation rate that formation of relevant metabolites is highly unlikely. Notwithstanding this consideration, it is recognised that even substances which are readily or inherently biodegradable may form metabolites which are (transiently) available and may lead to exposure under continuous releases. In such cases further (simulation) tests may be required if the PEC/PNEC is more than one and the risk assessment needs refinement in relation to metabolites.

4.2.4.1. Ready biodegradation (CDS)

Ready biodegradability tests are stringent tests which provide limited opportunity for biodegradation and acclimatisation to occur. It may be assumed that a chemical giving a positive result in a test of this type will rapidly biodegrade in the environment and therefore be classified

as 'readily biodegradable' in Annex VI of CLP. Tests on ready biodegradability are required for the core data set of active substances and are described in EC method C.4 A-F (Determination of 'Ready' Biodegradability) or the corresponding OECD Test Guideline 301 (Ready Biodegradability) A-F (see Chapter II Section 10.1.1.2).

Information on ready biodegradability tests and the interpretation of their results is summarised in chapters 2.3.6.4 and 2.3.6.5 of the TGD for new and existing substances (EU, 2003). Ready biodegradability tests provide information on ultimate degradation (mineralisation), which can be used to determine whether the parent compound is readily biodegradable or not. To make the results of ready tests useful for risk assessment, rate constants have been assigned to the results of the test. It is considered to be helpful to distinguish why a ready test has not been passed. It may be that the pass level (certain level of mineralisation within 28 days) is not reached and/or that the additional kinetic criterion of the 10-days window is failed. Different rate constants are assigned in these situations. The proposed rate constant for readily biodegradable substances can be found in the TGD for new and existing substances in tables 6 (STP, chapter 2.3.6.4), 7 (surface water, chapter 2.3.6.5) and 8 (soil, chapter 2.3.6.5) (EU, 2003).

4.2.4.2. Inherent biodegradability (CDS)

Inherent biodegradability tests are tests which allow prolonged exposure of the test compound to micro-organisms, a more favourable test compound/biomass ratio as well as chemical or other conditions, that favour biodegradation. A compound giving a positive result in a test of this type may be classified as "inherently biodegradable", but, because of the favourable conditions employed, its rapid and reliable biodegradation in the environment may not be assumed. Tests on inherent biodegradability are required for the core data set of active substances 'where appropriate', meaning if available. They are described in EC method C.9 (Biodegradation — Zahn-Wellens Test) or the corresponding OECD Test Guidelines 302 B (Inherent Biodegradability: Zahn-Wellens/ EVPA Test) or OECD 302 C (Inherent Biodegradability: Modified MITI Test (II)).

Core-data testing for inherent biodegradability may in general not be appropriate, since these tests do not provide adequate information for risk assessment purposes. Therefore, simulation tests are preferred instead of new tests on inherent biodegradability. Nevertheless, if inherent biodegradation data are available (which may well be the case for biocides which are already on the market), the output of the test can be used if the tests fulfil specific criteria:

Zahn-Wellens test:	Pass level must be reached within 7 days, log-phase should be no longer than 3 days, and percentage removal in the test before biodegradation occurs should be below 15 %.
MITI-II test:	Pass level must be reached within 14 days, log-phase should be no longer than 3 days.
SCAS test:	Even if a substance is biodegradable according to the SCAS test, the degradation rate is set to zero and further tests are generally required.

Information on inherent biodegradability tests and the interpretation of the results of the tests is summarised in in chapters 2.3.6.4 and 2.3.6.5 of the TGD for new and existing substances (EU, 2003). The proposed rate constant for inherently degradable substances can be found in TGD in tables 6 (STP, chapter 2.3.6.4), 7 (surface water, chapter 2.3.6.5) and 8 (soil, chapter 2.3.6.5).

4.2.5. Simulation tests

Simulation tests are tests which provide evidence of the rate of biodegradation under some environmentally relevant conditions. Tests of this type may be subdivided according to the environment they are designed to simulate a) biological treatment (aerobic); b) biological treatment (anaerobic); c) river; d) lake; e) estuary; f) sea; and g) soil.

Simulation tests may be performed directly, thus skipping the screening stage biodegradation tests. This may be required for biocides which are toxic to the inoculum (see Section 2.2 of this chapter). If a substance is not readily or inherently biodegradable, further refinement of the degradation rate and route is needed:

- For all environmental compartments which are directly exposed, a respective simulation test needs to be conducted. This is to ensure that a full environmental risk assessment can be performed for these directly exposed compartments (this full environmental risk assessment also needs to consider the environmental risks posed by any major metabolites or any ecotoxicologically relevant metabolites).
- Potential atmospheric deposition should also be taken into account.

Thus further conditions given in the following sections refer only to substances which are not readily or inherently biodegradable. If a substance is not readily biodegradable and either not vB or not classified as B or T, it may not be necessary to conduct simulation studies for the indirectly exposed environmental compartments. For the PBT assessment, the substance would thus be considered vP, but it would not have any regulatory consequences (as the substance is not in addition vB nor fulfils two (or even three) of the three PBT criteria). As soon as there is new information and this results in the substance being considered as B or T in addition to its classification as vP, it may become necessary to perform a P assessment. For the environmental risk assessment in the indirectly exposed compartments, the first tier assessment can be performed without the need for simulation studies (i.e. the risk assessment can focus on the active substance only, utilising information from the available core data, e.g. hydrolysis, photolysis etc.). A robust argument about the formation of potential metabolites of concern is required. Additional simulation studies in indirectly exposed compartments may be useful to refine the first tier risk assessment.

Any simulation test should at least fulfil the following criteria:

- give measured rates for primary degradation and an indication of the mineralisation potential;
- allow for quantification and identification of metabolites formed during the test;
- provide an indication of the degradation rates or persistence of the metabolites.

At this stage in the scheme, it becomes important to which compartment(s) the emission takes place. Simulation tests after indirect release are relevant for substances which do not degrade or dissipate in the first receiving compartment and thus are transported to consecutive compartments.

4.2.5.1. Sewage Treatment Plant (STP)

If the substance first enters an STP before release to the environment, an STP simulation test can be used to refine the initial risk assessment for STP or subsequently exposed compartments. The provided information on the degradation and the distribution of the substance in the respective compartments can be used as direct input parameters in calculation models.

For the relevant test methods, please follow guidance in Chapter II Section 10.1.3.1 (c).

4.2.5.2. Water/sediment

If the biocide is directly emitted to water, a water simulation test is required.

A water/sediment simulation test shall be performed for substances with K_p (sediment) > 2000 (with quantification of bound residues) for direct or indirect emission to water/sediment systems.

If the substance has a water solubility well below 1 µg/L, depending on the physico-chemical properties, it may not be warranted to conduct a water simulation study. As substances with such low water solubility may often be adsorptive, rather a water/sediment simulation study than a water simulation study may be required.

There might also be a need to perform a water/sediment simulation study when the surface water is directly exposed in case no adsorption/desorption test with sediment is available (please refer to Section 3 of this chapter).

For the relevant test methods for water simulation studies, please follow guidance in Chapter II Section 10.1.3.2 (a).

The water/sediment simulation tests should be performed according to test methods given in Chapter II Section 10.1.3.2 (b).

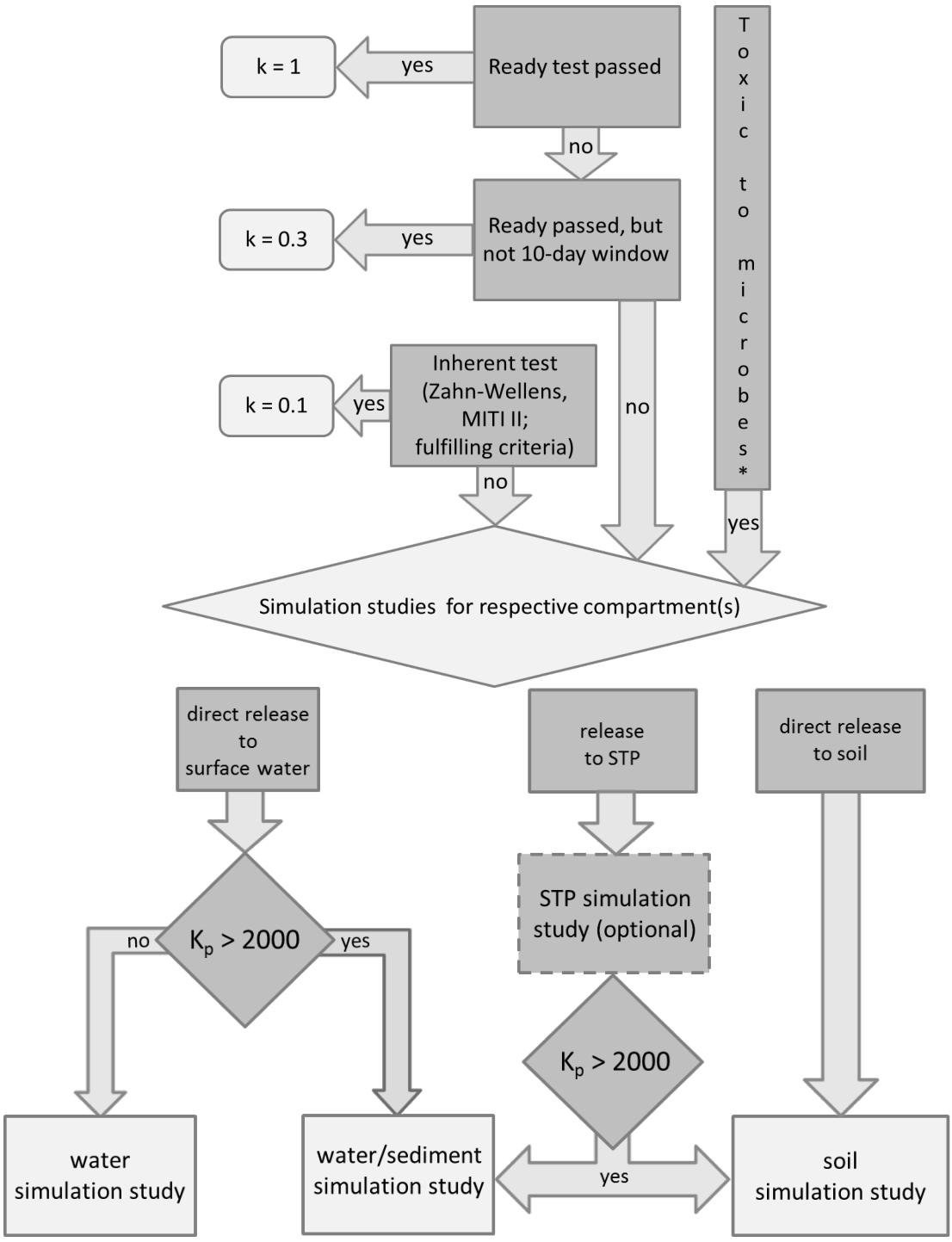
For the assessment of substances released to marine environments, the test system has to be adapted accordingly. Chapter V provides more guidance on the product-types for which this is the case, and Chapter II Section 10.1.3.3 describes the relevant seawater biodegradation test methods.

4.2.5.3. Soil

If the biocide is directly applied or emitted to soil, a soil simulation test is required. The route(s) of degradation should be studied in one of the soils tested. Such a test should be done in three different additional soil types which, depending on the characteristics of the substance, should cover a wide range of relevant soil characteristics.

If the soil compartment is indirectly exposed, but the substance has a K_p > 2000, it partitions to STP sludge which is spread on soil. Therefore soil simulation degradation testing is warranted in these cases. For the relevant test methods, please refer to Chapter II Section 10.2.1.

An outdoor soil lysimeter study/field study may be relevant to complete the soil testing strategy, e. g. according to OECD Guidance Document 22 for the performance of outdoor monolith lysimeter studies. See Chapter II Section 10.2.6 and Chapter IV Section 3 for further guidance.



* please refer to Section 2.2 of this chapter

Figure 5 Biocides biodegradation test strategy

4.3. Testing strategy for adsorption/desorption

To perform the environmental risk assessment, an adsorption coefficient is necessary. Depending on the environmental pathways, it needs to be decided which test(s) may be adequate:
In general, a screening test on adsorption/desorption is required according to the test methods referred to in Chapter II Section 10.1.2. Although not explicitly mentioned in the guideline the handling procedure can also be applied to sediments or activated sludge.

A specific study with sediments or sewage sludge, if adsorption to these is of concern, may be provided in case of direct exposure to sediment for a refinement of the initial risk assessment or if no water/sediment study is available (see also Section 2.5.2 of this chapter). Please refer to Chapter II Section 10.1.4 for the relevant test methods.

In case of direct exposure to soil a full scale study (isotherms, mass balance, desorption) with soil needs to be provided unless it is shown to be readily biodegradable. In case of indirect exposure (e.g. spreading of contaminated sewage sludge on land) to soil this study may be conducted to refine the initial risk assessment.

A full scale adsorption test with soils may also be appropriate to refine the PEC value in those cases where modelling results indicate that relevant concentrations of the substance may reach groundwater. Please refer to Chapter II Section 10.2.4 for the relevant test methods and the selection of suitable soils.

To further refine the risk assessment for soil or subsequently groundwater, soil column leaching studies can provide reliable and useful lower limits of the K_{OC} if the expected K_{OC} value is less than 25 L/kg. The test should provide sufficient data to evaluate the mobility and leaching potential of the active substance. Please refer to Chapter II Section 10.2.6.1 for the relevant test methods.

Where it is indicated from data on adsorption and degradation in soil that relevant amounts of a substance may reach groundwater it may become necessary to carry out an outdoor confirmatory study. For guidance on how to perform a long term study on mobility of a substance in undisturbed soil under outdoor conditions refer to Chapter II Sections 10.2.6.2 and 10.2.6.3.

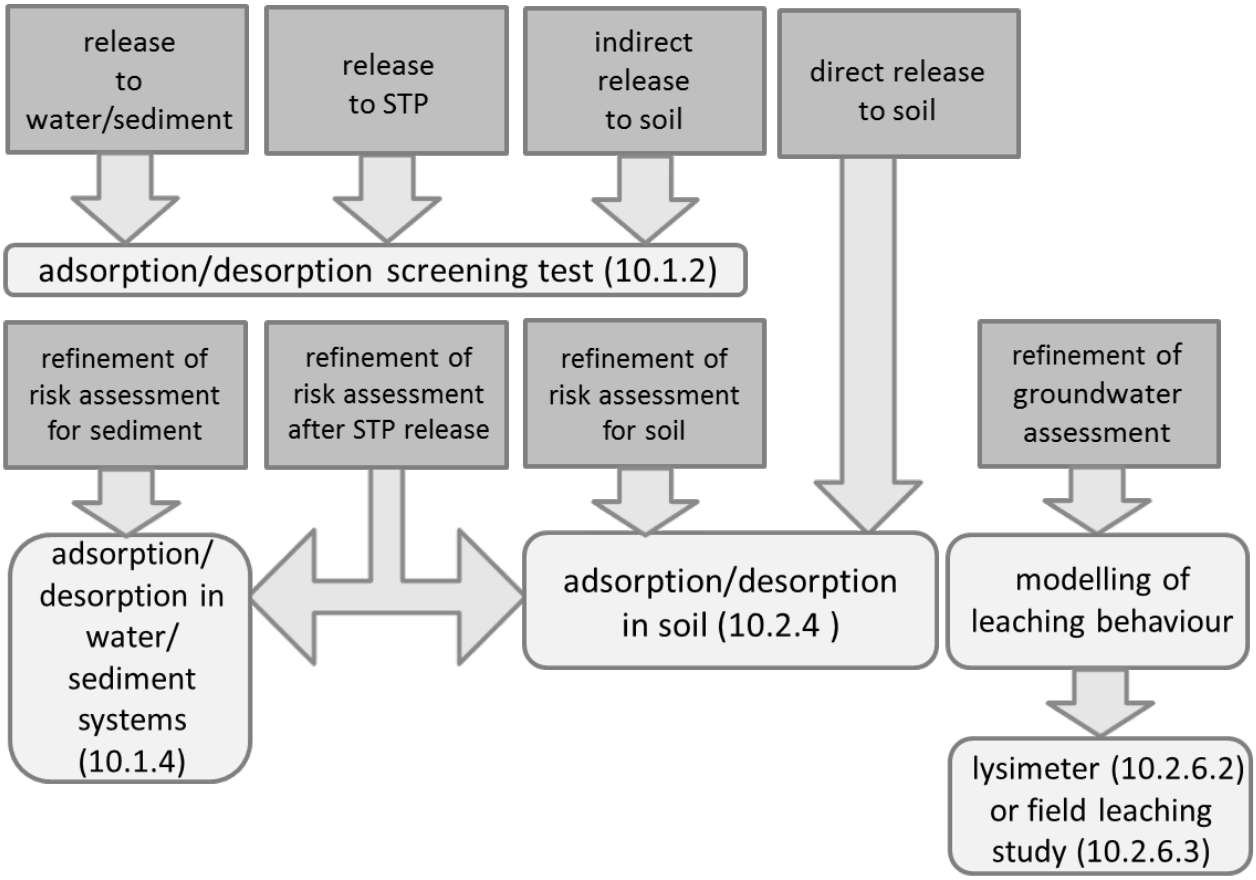


Figure 6 Testing strategy for adsorption/desorption and mobility

V. PRODUCT-TYPE SPECIFIC ADDITIONAL DATA SET FOR ACTIVE SUBSTANCES AND BIOCIDAL PRODUCTS REGARDING ECOTOXICOLOGICAL PROFILE, INCLUDING ENVIRONMENTAL FATE AND BEHAVIOUR

A risk assessment is performed on the basis of the data requested in Annexes II and III (information requirements for the active substance and the biocidal product, respectively). Based on the product-type, for which an active substance will be used, and thus the emission pathways, additional information to those required for the core data set (CDS) might be necessary to be able to perform an initial risk assessment.

These data are usually required to be delivered together with the CDS. If the initial risk assessment shows an indication of risk for man or the environment, the applicant should conduct further studies according to the guidance in Chapters II, III or IV (as applicable) in order to refine the risk assessment and reach a conclusion.

Detailed exposure scenarios have not yet been developed for all 22 product-types or all uses within a product-type. Thus, other uses might exist that give rise to direct exposure, for which additional tests might also be necessary. Therefore, Chapter V would need refinement when exposure scenarios are available for all product-types.

If brackish or marine environments are exposed, in addition to the freshwater ecotoxicological tests which are CDS, additional tests should be performed with species representative of brackish or marine environments and habitats. It should be considered to conduct long term tests as this may reduce the uncertainty of the effect assessment.

Long term ecotoxicity data is required if there is potential continuous emission to the terrestrial or the aquatic environment, e.g. because of leaching from a biocidal product or a treated article. If the release is intermittent[12] or the intended use is limited to small or closed spaces with insignificant release, initial short-term tests providing acute ecotoxicity data may be sufficient to meet the additional testing requirements, unless there are concerns that chronic effects may arise when taking into account, for example the mode of action or the expected environmental fate of the substance. For this situation consultations with the evaluation competent authority or ECHA should be sought before further testing is conducted.

In the following sections, for each product-type, those tests are listed which are required in addition to the CDS. For further instructions which test is to be preferred in the case of a number of possible tests, please consult the respective sections in Chapters II and III.

Here only the typical uses as depicted in the available emission scenario documents are taken into account. If there are emission pathways for the biocidal products which differ from these emission pathways; different, additional or less information may be necessary. In case of any confusion concerning the information requirements for any specific active substance or biocidal product, please contact ECHA or the evaluating competent authority.

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[12] Intermittent release: intermittent but only recurring infrequently i.e. less than once per month and for no more than 24 hours (e.g. batch processes only required for a short period of the year)

An overview of the data requirements for the active substance can be found in Table 5 below.

5.1. Guidance on product-type specific additional data set for (chemical) active substances

Product-type 1: Human hygiene biocidal products

The release to the environment is usually diffuse via STP. No supplementary test data regarding the ecotoxicological and fate profile beyond those listed in the core data set need to be generated in order to perform a preliminary risk assessment for this emission pathway.

Product-type 2: Private area and health area disinfectants

Due to the potential continuous release to surface water, chronic aquatic toxicity data is normally required for this product-type:

9.1.3	Growth inhibition test on algae (if no chronic data (NOEC or EC_{10}) is available from the core data set)
9.1.6.1	Long term toxicity testing on fish
9.1.6.2	Long term toxicity testing on invertebrates

For substances to be used as soil or solid waste disinfectants, direct release to soil is to be taken into account. In such case it is necessary to perform initial or, if there is potential continuous exposure, long term terrestrial effects tests:

9.2.1	Tests with soil micro-organisms
9.2.2/9.3.1	Tests with earthworms or other soil-dwelling non-target invertebrates
9.2.3/9.3	Toxicity to plants

Furthermore, it is necessary to conduct studies on fate and behaviour (if not readily biodegradable) in case of direct emission to soil:

10.2.1	Laboratory study on rate and route of degradation including identification of the processes involved and identification of any metabolites and degradation products in one soil type (unless pH dependent route) under appropriate conditions. Laboratory studies on rate of degradation in three additional soil types
10.2.4	Adsorption and desorption in at least three soil types and, where relevant, adsorption and desorption of metabolites and degradation products

Product-type 3: Veterinary hygiene biocidal products

Due to potential continuous release to surface water, chronic aquatic toxicity data would normally be required for this product-type:

9.1.3	Growth inhibition test on algae (if no chronic data (NOEC or EC_{10}) is available from the core data set)
9.1.6.1	Long term toxicity testing on fish
9.1.6.2	Long term toxicity testing on invertebrates

Releases into manure storage facilities are possible. In such case it is necessary to perform a test for estimation of fate in the manure storage facility:

10.1.3.4	Biodegradation during manure storage

It is necessary to perform initial or, if there is potential continuous exposure, long term terrestrial effects tests for the soil compartment after manure application:

9.2.1	Tests with soil micro-organisms
9.2.2/9.3.1	Tests with earthworms or other soil-dwelling non-target invertebrates

9.2.3/9.3 Tests with plants

Furthermore, it is necessary to conduct studies on fate and behaviour in soil after manure application (if not readily biodegradable):

10.2.1 Laboratory study on rate and route of degradation including identification of the processes involved and identification of any metabolites and degradation products in one soil type (unless pH dependent route) under appropriate conditions. Laboratory studies on rate of degradation in three additional soil types.

10.2.4 Adsorption and desorption in at least three soil types and, where relevant, adsorption and desorption of metabolites and degradation products

For use in poultry farms, where wild birds are attracted, a risk assessment for birds is necessary:

9.4 Effects on birds

If the substance is to be used in freshwater or marine fish nurseries, additional aquatic ecotoxicity tests need to be performed where relevant with marine/brackish species and biodegradation tests are required. If there is potential continuous release, long term ecotoxicity tests are normally required:

9.1.1/9.1.6.1 Tests with fish (marine/brackish species)

9.1.2/9.1.6.2 Tests with invertebrates (marine/brackish species)

9.1.3 Growth inhibition test on algae (marine/brackish species)

9.1.8 Tests with any other specific, non-target organisms (flora and fauna) believed to be at risk

10.1.3.2 Biodegradation in freshwater

10.1.3.3 Biodegradation in sea water

Product-type 4: Food and feed area disinfectants

Due to the potential continuous release to surface water, chronic aquatic toxicity data would normally be required for this product-type:

9.1.3 Growth inhibition test on algae (if no chronic data (NOEC or EC_{10}) is available from the core data set)

9.1.6.1 Long term toxicity testing on fish

9.1.6.2 Long term toxicity testing on invertebrates

Product-type 5: Drinking water disinfectants

Due to the potential continuous release to surface water, chronic aquatic toxicity data would normally be required for this product-type:

9.1.3 Growth inhibition test on algae (if no chronic data (NOEC or EC_{10}) is available from the core data set)

9.1.6.1 Long term toxicity testing on fish

9.1.6.2 Long term toxicity testing on invertebrates

Releases into manure storage facilities are possible if the active substance is used in disinfectants for animal drinking water. In such case it is necessary to perform a test for the estimation of fate in the manure storage facility:

10.1.3.4 Biodegradation during manure storage

It is also necessary to perform initial or, if there is potential continuous exposure, long term terrestrial effects tests in soil after manure application:

9.2.1 Tests with soil micro-organisms

9.2.2/9.3.1 Tests with earthworms or other soil-dwelling non-target invertebrates

9.2.3/9.3 Tests with plants

Furthermore, it is necessary to conduct studies on fate and behaviour in soil after manure application (if not readily biodegradable):

10.2.1 Laboratory study on rate and route of degradation including identification of the processes involved and identification of any metabolites and degradation products in one soil type (unless pH dependent route) under appropriate conditions. Laboratory studies on rate of degradation in three additional soil types

10.2.4 Adsorption and desorption in at least three soil types and, where relevant, adsorption and desorption of metabolites and degradation products

Product-type 6: In-can preservatives

Due to the potential continuous release to surface water, chronic aquatic toxicity data would normally be required for this product-type:

9.1.3 Growth inhibition test on algae (if no chronic data (NOEC or EC_{10}) is available from the core data set)

9.1.6.1 Long term toxicity testing on fish

9.1.6.2 Long term toxicity testing on invertebrates

Where direct releases to the terrestrial compartment occur (e.g. via leaching), it is necessary to perform initial or, if there is potential continuous exposure, long term terrestrial effects tests:

9.2.1 Tests with soil micro-organisms

9.2.2/9.3.1 Tests with earthworms or other soil-dwelling non-target invertebrates

9.2.3/9.3 Tests with plants

Furthermore, it is necessary to conduct studies on fate and behaviour in soil (if not readily biodegradable):

10.2.1 Laboratory study on rate and route of degradation including identification of the processes involved and identification of any metabolites and degradation products in one soil type (unless pH dependent route) under appropriate conditions. Laboratory studies on rate of degradation in three additional soil types

10.2.4 Adsorption and desorption in at least three soil types and, where relevant, adsorption and desorption of metabolites and degradation products

Product-type 7: Film preservatives

Due to the potential continuous release to surface water, chronic aquatic toxicity data would normally be required for this product-type:

9.1.3 Growth inhibition test on algae (if no chronic data (NOEC or EC_{10}) is available from the core data set)

9.1.6.1 Long term toxicity testing on fish

9.1.6.2 Long term toxicity testing on invertebrates

Where direct releases to the terrestrial compartment occur (e.g. via leaching), it is necessary to perform initial or, if there is potential continuous exposure, long term terrestrial effects tests:

9.2.1 Tests with soil micro-organisms

9.2.2/9.3.1 Tests with earthworms or other soil-dwelling non-target invertebrates

9.2.3/9.3 Tests with plants

Furthermore, it is necessary to conduct studies on fate and behaviour in soil (if not readily biodegradable):

10.2.1 Laboratory study on rate and route of degradation including identification of the processes involved and identification of any metabolites and degradation products in one soil type (unless pH dependent route) under appropriate conditions. Laboratory studies on rate of degradation in three additional soil types
10.2.4 Adsorption and desorption in at least three soil types and, where relevant, adsorption and desorption of metabolites and degradation products

Product-type 8: Wood preservatives

Due to the potential continuous release to surface water, chronic aquatic toxicity data would normally be required for this product-type:
9.1.3 Growth inhibition test on algae (if no chronic data (NOEC or EC_{10}) is available from the core data set)
9.1.6.1 Long term toxicity testing on fish
9.1.6.2 Long term toxicity testing on invertebrates

In case of direct releases to a freshwater compartment (e.g. in use classes (UC) 3 and 4b), an aquatic degradation test is required:
10.1.3.2 Biodegradation in freshwater

Direct releases to the terrestrial compartment are possible (e.g. in UC 3 and 4a). It is necessary to perform initial or, if there is potential continuous exposure, long term terrestrial effects tests:
9.2.1 Tests with soil micro-organisms
9.2.2/9.3.1 Tests with earthworms or other soil-dwelling non-target invertebrates
9.2.3/9.3 Tests with plants

Furthermore, it is necessary to conduct studies on fate and behaviour in soil (if not readily biodegradable):
10.2.1 Laboratory study on rate and route of degradation including identification of the processes involved and identification of any metabolites and degradation products in one soil type (unless pH dependent route) under appropriate conditions. Laboratory studies on rate of degradation in three additional soil types
10.2.4 Adsorption and desorption in at least three soil types and, where relevant, adsorption and desorption of metabolites and degradation products

If the substance is to be used for wood in UC 5 (salt water) defined in the standard CEN 335-1 (CEN 1992), the aquatic toxicity tests need to be performed additionally with marine/brackish species and a saltwater biodegradation test is required:
9.1.1/9.1.6.1 Tests with fish (marine/brackish species)
9.1.2/9.1.6.2 Tests with invertebrates (marine/brackish species)
9.1.3 Growth inhibition test on algae (marine/brackish species)
9.1.8 Tests with any other specific, non-target organisms (flora and fauna) believed to be at risk
10.1.3.3 Biodegradation in sea water

Product-type 9: Preservatives for fibres, leather, rubber and polymerised material

Due to the potential continuous release to surface water, chronic aquatic toxicity data would normally be required for this product-type:
9.1.3 Growth inhibition test on algae (if no chronic data (NOEC or EC_{10}) is available from the core data set)
9.1.6.1 Long term toxicity testing on fish

9.1.6.2 Long term toxicity testing on invertebrates

Where direct releases to the terrestrial compartment occur (e.g. via leaching) it is necessary to perform initial or, if there is potential continuous exposure, long term terrestrial effects tests:
9.2.1 Tests with soil micro-organisms
9.2.2/9.3.1 Tests with earthworms or other soil-dwelling non-target invertebrates
9.2.3/9.3 Tests with plants

Furthermore, it is necessary to conduct studies on fate and behaviour in soil (if not readily biodegradable):
10.2.1 Laboratory study on rate and route of degradation including identification of the processes involved and identification of any metabolites and degradation products in one soil type (unless pH dependent route) under appropriate conditions. Laboratory studies on rate of degradation in three additional soil types
10.2.4 Adsorption and desorption in at least three soil types and, where relevant, adsorption and desorption of metabolites and degradation products

Product-type 10: Masonry preservatives

Due to the potential continuous release to surface water, chronic aquatic toxicity data would normally be required for this product-type:
9.1.3 Growth inhibition test on algae (if no chronic data (NOEC or EC_{10}) is available from the core data set)
9.1.6.1 Long term toxicity testing on fish
9.1.6.2 Long term toxicity testing on invertebrates

For remedial treatment as well as spray application in general, high releases to the terrestrial compartment are possible. It is necessary to perform initial or, if there is potential continuous exposure, long term terrestrial effects tests:
9.2.1 Tests with soil micro-organisms
9.2.2/9.3.1 Tests with earthworms or other soil-dwelling non-target invertebrates
9.2.3/9.3 Tests with plants

Furthermore, it is necessary to conduct studies on fate and behaviour in soil (if not readily biodegradable):
10.2.1 Laboratory study on rate and route of degradation including identification of the processes involved and identification of any metabolites and degradation products in one soil type (unless pH dependent route) under appropriate conditions. Laboratory studies on rate of degradation in three additional soil types
10.2.4 Adsorption and desorption in at least three soil types and, where relevant, adsorption and desorption of metabolites and degradation products

Product-type 11: Preservatives for liquid-cooling and processing systems

Due to the potential continuous release to surface water, chronic aquatic toxicity data would normally be required for this product-type:
9.1.3 Growth inhibition test on algae (if no chronic data (NOEC or EC_{10}) is available from the core data set)
9.1.6.1 Long term toxicity testing on fish
9.1.6.2 Long term toxicity testing on invertebrates

For substances to be used in cooling systems with open cooling towers, a high water discharge to air and subsequent deposition onto soil is possible. In these cases, it is necessary to perform initial or, if there is potential continuous exposure, long term terrestrial effects tests:

9.2.1 Tests with soil micro-organisms
9.2.2/9.3.1 Tests with earthworms or other soil-dwelling non-target invertebrates
9.2.3/9.3 Tests with plants

Furthermore, it is necessary to conduct studies on fate and behaviour in soil (if not readily biodegradable):

10.2.1 Laboratory study on rate and route of degradation including identification of the processes involved and identification of any metabolites and degradation products in one soil type (unless pH dependent route) under appropriate conditions. Laboratory studies on rate of degradation in three additional soil types
10.2.4 Adsorption and desorption in at least three soil types and, where relevant, adsorption and desorption of metabolites and degradation products

For substances to be used in the cooling systems releasing their cooling water directly to a freshwater compartment (e.g a river or a lake), a degradation test in freshwater is required:

10.1.3.2 Biodegradation in freshwater

For substances to be used on sites situated near the coast and using marine/brackish water in their cooling systems, the aquatic toxicity tests need to be performed additionally with marine/brackish species and a saltwater biodegradation test is required as well:

9.1.1/9.1.6.1 Tests with fish (marine/brackish species)
9.1.2/9.1.6.2 Tests with invertebrates (marine/brackish species)
9.1.3 Growth inhibition test on algae (marine/brackish species)
9.1.8 Tests with any other specific, non-target organisms (flora and fauna) believed to be at risk
10.1.3.3 Biodegradation in sea water

Product-type 12: Slimicides

Due to the potential continuous release to surface water, chronic aquatic toxicity data would normally be required for this product-type:

9.1.3 Growth inhibition test on algae (if no chronic data (NOEC or EC_{10}) is available from the core data set)
9.1.6.1 Long term toxicity testing on fish
9.1.6.2 Long term toxicity testing on invertebrates

For inland use of drilling and oil recovery preservatives, it is necessary to perform initial or, if there is potential continuous exposure, long term terrestrial effects tests:

9.2.1 Tests with soil micro-organisms
9.2.2/9.3.1 Tests with earthworms or other soil-dwelling non-target invertebrates
9.2.3/9.3 Tests with plants

Furthermore, it is necessary to conduct studies on fate and behaviour in soil (if not readily biodegradable):

10.2.1 Laboratory study on rate and route of degradation including identification of the processes involved and identification of any metabolites and degradation products in one soil type (unless pH dependent route) under appropriate conditions. Laboratory studies on rate of degradation in three additional soil types
10.2.4 Adsorption and desorption in at least three soil types and, where relevant, adsorption and desorption of metabolites and degradation products

For offshore uses, the aquatic toxicity tests need to be performed additionally with marine/brackish species and a saltwater biodegradation test is required as well:

9.1.1/9.1.6.1 Tests with fish (marine/brackish species)
9.1.2/9.1.6.2 Tests with invertebrates (marine/brackish species)
9.1.3 Growth inhibition test on algae (marine/brackish species)
9.1.8 Tests with any other specific, non-target organisms (flora and fauna) believed to be at risk
10.1.3.3 Biodegradation in sea water

Product-type 13: Working or cutting fluid preservatives

Due to the potential continuous release to surface water, chronic aquatic toxicity data would be necessary for this product-type, unless the release is intermittent or the intended use is limited to closed spaces with insignificant aquatic release:

9.1.6.1 Long term toxicity testing on fish
9.1.6.2 Long term toxicity testing on invertebrates
9.1.3 Growth inhibition test on algae (if no NOEC is available from the core data set)

Product-type 14: Rodenticides

For products to be used in animal housing, releases to manure storage facilities are possible. A study on biodegradation during manure storage is necessary:

10.1.3.4 Biodegradation during manure storage

It is also necessary to perform initial or, if there is potential continuous exposure, long term terrestrial effects tests in soil after manure application:

9.2.1 Tests with soil micro-organisms
9.2.2/9.3.1 Tests with earthworms or other soil-dwelling non-target invertebrates
9.2.3/9.3 Tests with plants

For substances to be used in direct contact to soil or in case of manure application from treated animal housings it is necessary to conduct studies on fate and behaviour (if not readily biodegradable):

10.2.1 Laboratory study on rate and route of degradation including identification of the processes involved and identification of any metabolites and degradation products in one soil type (unless pH dependent route) under appropriate conditions. Laboratory studies on rate of degradation in three additional soil types
10.2.4 Adsorption and desorption in at least three soil types and, where relevant, adsorption and desorption of metabolites and degradation products

If used outdoors in the form of baits, granulates or powder, a risk assessment for birds is necessary.

9.4 Effects on birds

Product-type 15: Avicides

For products to be used in animal housing, releases to manure storage facilities are possible. A study on biodegradation during manure storage is necessary:

10.1.3.4 Biodegradation during manure storage

It is also necessary to perform initial or, if there is potential continuous exposure, long term terrestrial effects tests in soil after manure application:

9.2.1 Tests with soil micro-organisms

9.2.2/9.3.1 Tests with earthworms or other soil-dwelling non-target invertebrates
9.2.3/9.3 Tests with plants

Furthermore, it is necessary to conduct studies on fate and behaviour in soil after manure application (if not readily biodegradable):
10.2.1 Laboratory study on rate and route of degradation including identification of the processes involved and identification of any metabolites and degradation products in one soil type (unless pH dependent route) under appropriate conditions. Laboratory studies on rate of degradation in three additional soil types
10.2.4 Adsorption and desorption in at least three soil types and, where relevant, adsorption and desorption of metabolites and degradation products

Product-type 16: Molluscicides, vermicides and products to control other invertebrates

Due to the potential continuous release to surface water, chronic aquatic toxicity data would normally be required for this product-type, unless the release is intermittent or the intended use is limited to closed spaces with insignificant aquatic release:
9.1.3 Growth inhibition test on algae (if no chronic data (NOEC or EC_{10}) is available from the core data set)
9.1.6.1 Long term toxicity testing on fish
9.1.6.2 Long term toxicity testing on invertebrates

For products to be used in animal housing, releases to manure storage facilities are possible. A study on biodegradation during manure storage is necessary:
10.1.3.4 Biodegradation during manure storage

For substances to be used in direct contact to soil or in case of manure application from treated animal housings it is necessary to conduct studies on fate and behaviour (if not readily biodegradable):
9.2.1 Tests with soil micro-organisms
9.2.2/9.3.1 Tests with earthworms or other soil-dwelling non-target invertebrates
9.2.3/9.3 Tests with plants

Furthermore, it is necessary to conduct studies on fate and behaviour in soil (if not readily biodegradable):
10.2.1 Laboratory study on rate and route of degradation including identification of the processes involved and identification of any metabolites and degradation products in one soil type (unless pH dependent route) under appropriate conditions. Laboratory studies on rate of degradation in three additional soil types
10.2.4 Adsorption and desorption in at least three soil types and, where relevant, adsorption and desorption of metabolites and degradation products

If used outside of buildings in the form of baits, granulates or powder, a risk assessment for birds is necessary
9.4 Effects on birds

For molluscicides used in marine waters, the aquatic toxicity tests need to be performed additionally with marine/brackish species and a saltwater biodegradation test is required as well:
9.1.1/9.1.6.1 Tests with fish (marine/brackish species)
9.1.2/9.1.6.2 Tests with invertebrates (marine/brackish species)
9.1.3 Growth inhibition test on algae (marine/brackish species)

9.1.8 Tests with any other specific, non-target organisms (flora and fauna) believed to be at risk
10.1.3.3 Biodegradation in sea water

Product-type 17: Piscicides

Chronic aquatic toxicity data would normally be required for this product-type:
9.1.3 Growth inhibition test on algae (if no chronic data (NOEC or EC_{10}) is available from the core data set)
9.1.6.1 Long term toxicity testing on fish
9.1.6.2 Long term toxicity testing on invertebrates

As well as aquatic degradation tests in case that direct releases to the freshwater compartment are possible:
10.1.3.2 Biodegradation in freshwater

If the substance is to be used in a marine environment, the aquatic toxicity tests need to be performed additionally with marine/brackish species and a saltwater biodegradation test is required as well:
9.1.1/9.1.6.1 Tests with fish (marine/brackish species)
9.1.2/9.1.6.2 Tests with invertebrates (marine/brackish species)
9.1.3 Growth inhibition test on algae (marine/brackish species)
9.1.8 Tests with any other specific, non-target organisms (flora and fauna) believed to be at risk
10.1.3.3 Biodegradation in sea water

Product-type 18: Insecticides, acaricides and products to control other arthropods

Due to the potential continuous release to surface water, chronic aquatic toxicity data would normally be required for this product-type:
9.1.3 Growth inhibition test on algae (if no chronic data (NOEC or EC_{10}) is available from the core data set)
9.1.6.1 Long term toxicity testing on fish
9.1.6.2 Long term toxicity testing on invertebrates

For products to be used in animal housing, releases to manure storage facilities are possible. A study on biodegradation during manure storage is necessary:
10.1.3.4 Biodegradation during manure storage

For products used outdoors as well as products to be used by gassing, fogging or fumigation, release to soil is possible. It is necessary to perform initial or, if there is potential continuous exposure, long term terrestrial effects tests, also in case of manure application:
9.2.1 Tests with soil micro-organisms
9.2.2/9.3.1 Tests with earthworms or other soil-dwelling non-target invertebrates
9.2.3/9.3 Tests with plants

Furthermore, it is necessary to conduct studies on fate and behaviour in soil (if not readily biodegradable):
10.2.1 Laboratory study on rate and route of degradation including identification of the processes involved and identification of any metabolites and degradation products in one soil type (unless pH dependent route) under appropriate conditions. Laboratory studies on rate of degradation in three additional soil types

10.2.4 Adsorption and desorption in at least three soil types and, where relevant, adsorption and desorption of metabolites and degradation products

If used outdoors in the form of baits, granulates or powder, a risk assessment for birds is necessary:
9.4 Effects on birds

Furthermore, tests with bees are required and tests with additional insects or other arthropods may also be requested depending *e.g.* on the exposure route:
9.5 Tests with arthropods
9.5.1 Tests with honeybees
9.5.2 Tests with other non-target terrestrial arthropods, e.g. predators

Product-type 19: Repellents and attractants

Due to the potential continuous release to surface water, chronic aquatic toxicity data would normally be required for this product-type:
9.1.3 Growth inhibition test on algae (if no chronic data (NOEC or EC_{10}) is available from the core data set)
9.1.6.1 Long term toxicity testing on fish
9.1.6.2 Long term toxicity testing on invertebrates

Aquatic degradation tests are necessary, if direct releases to the freshwater compartment are possible:
10.1.3.2 Biodegradation in freshwater (a. Aerobic aquatic degradation study or b. Water/sediment degradation test).

For products to be used in animal housing, releases to manure storage facilities are possible. A study on biodegradation during manure storage is necessary:
10.1.3.4 Biodegradation during manure storage

It is also necessary to perform initial or, if there is potential continuous exposure, long term terrestrial effects tests in soil after manure application:
9.2.1 Tests with soil micro-organisms
9.2.2/9.3.1 Tests with earthworms or other soil-dwelling non-target invertebrates
9.2.3/9.3 Tests with plants

Furthermore, it is necessary to conduct studies on fate and behaviour in soil after manure application (if not readily biodegradable):
10.2.1 Laboratory study on rate and route of degradation including identification of the processes involved and identification of any metabolites and degradation products in one soil type (unless pH dependent route) under appropriate conditions. Laboratory studies on rate of degradation in three additional soil types
10.2.4 Adsorption and desorption in at least three soil types and, where relevant, adsorption and desorption of metabolites and degradation products

If the substance is to be used as a shark repellent, the aquatic toxicity tests need to be performed additionally with marine/brackish species and a saltwater biodegradation test is required as well:
9.1.1/9.1.6.1 Tests with fish (marine/brackish species)
9.1.2/9.1.6.2 Tests with invertebrates (marine/brackish species)
9.1.3 Growth inhibition test on algae (marine/brackish species)
9.1.8 Tests with any other specific, non-target organisms (flora and fauna) believed to be at risk

10.1.3.3 Biodegradation in sea water

Product-type 20: Control of other vertebrates

For products to be used in animal housing, releases to manure storage facilities are possible. A study on biodegradation during manure storage is necessary:
10.1.3.4 Biodegradation during manure storage

For products used outdoors in contact with soil, direct release to soil is possible. It is necessary to perform initial or, if there is potential continuous exposure, long term terrestrial effects tests, also in case of manure application:
9.2.1 Tests with soil micro-organisms
9.2.2/9.3.1 Tests with earthworms or other soil-dwelling non-target invertebrates
9.2.3/9.3 Tests with plants

Furthermore, it is necessary to conduct studies on fate and behaviour in soil after manure application (if not readily biodegradable):
10.2.1 Laboratory study on rate and route of degradation including identification of the processes involved and identification of any metabolites and degradation products in one soil type (unless pH dependent route) under appropriate conditions. Laboratory studies on rate of degradation in three additional soil types
10.2.4 Adsorption and desorption in at least three soil types and, where relevant, adsorption and desorption of metabolites and degradation products

If used outside of buildings in the form of baits, granulates or powder, a risk assessment for birds is necessary
9.4 Effects on birds

Product-type 21: Antifouling products

Aquatic degradation tests for freshwater are necessary, if direct releases to the freshwater compartment are possible:
10.1.3.2 Biodegradation in freshwater

Chronic aquatic toxicity data would be necessary for this product-type, if continuous direct releases to the freshwater compartment are possible during use:
9.1.3 Growth inhibition test on algae (if no chronic data (NOEC or EC_{10}) is available from the core data set)
9.1.6.1 Long term toxicity testing on fish
9.1.6.2 Long term toxicity testing on invertebrates

If the substance is to be used in a marine environment, the aquatic toxicity tests need to be performed additionally with marine/brackish species and a saltwater biodegradation test is required as well:
9.1.1/9.1.6.1 Tests with fish (marine/brackish species)
9.1.2/9.1.6.2 Tests with invertebrates (marine/brackish species)
9.1.3 Growth inhibition test on algae (marine/brackish species)
9.1.8 Tests with any other specific, non-target organisms (flora and fauna) believed to be at risk
10.1.3.3 Biodegradation in sea water

Several additional tests with marine/brackish species are required to accurately assess the risks for these substances:

9.1.7 Bioaccumulation tests in an appropriate aquatic species (fish as well as invertebrate species)
9.1.9 Tests on sediment dwelling organisms
9.1.10 Tests on aquatic macrophytes

For substances, which can have direct emission to soil, it is necessary to perform initial or, if there is potential continuous exposure, long term terrestrial effects tests:
9.2.1 Tests with soil micro-organisms
9.2.2/9.3.1 Tests with earthworms or other soil-dwelling non-target invertebrates
9.2.3/9.3 Tests with plants

Furthermore, it is necessary to conduct studies on fate and behaviour in soil (if not readily biodegradable):
10.2.1 Laboratory study on rate and route of degradation including identification of the processes involved and identification of any metabolites and degradation products in one soil type (unless pH dependent route) under appropriate conditions. Laboratory studies on rate of degradation in three additional soil types
10.2.4 Adsorption and desorption in at least three soil types and, where relevant, adsorption and desorption of metabolites and degradation products

Product-type 22: Embalming and taxidermist fluids

For substances to be used in direct contact to soil, it is necessary to conduct studies on fate and behaviour in soil (if not readily biodegradable; initial tests on soil organisms are not required since the release occurs in deeper soil layers and not on the soil surface):
10.2.1 Laboratory study on rate and route of degradation including identification of the processes involved and identification of any metabolites and degradation products in one soil type (unless pH dependent route) under appropriate conditions. Laboratory studies on rate of degradation in three additional soil types
10.2.4 Adsorption and desorption in at least three soil types and, where relevant, adsorption and desorption of metabolites and degradation products

Table 8 An overview of product-type specific additional information requirements for active substances

(BPR Annex II)

\+ = required for **specific uses** within the respective PT (triggered by emission pathways).
(+) = required for **specific uses** within the respective PT (triggered by emission pathways), if not readily biodegradable

Please refer also to the text for the respective PT in relation to the specific uses and their emission pathways triggering the information requirements.
Please refer also to Chapter IV Testing Strategies.

Product-type:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
9. ECOTOXICOLOGICAL STUDIES																						
9.1. Toxicity to Aquatic Organisms																						
9.1.1. Short-term toxicity testing on fish			+					+			+	+				+	+		+			
9.1.2. Short-term toxicity testing on aquatic invertebrates			+					+			+	+				+	+		+			
9.1.3. Growth inhibition study on algae [13]		+	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+		+	
9.1.6.1. Long term toxicity testing on fish		+	+	+	+	+	+	+	+	+	+	+	+			+	Ap	+	+		+	
9.1.6.2 Long term toxicity testing on invertebrates		+	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+		+	
9.1.7. Bioaccumulation in an appropriate aquatic species[14]																					+	

[13] This study is a core data requirement but is noted here again since it is required if no NOEC is available from the core data set
[14] Two studies are required (e.g. for PT21): Bioaccumulation in an appropriate species of fish and in an appropriate invertebrate species

Product-type:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
9.1.8. Effects on any other specific, non-target organisms (flora and fauna) believed to be at risk[15]			+					+			+	+				+	+		+		+	
9.1.9. Studies on sediment dwelling organisms																					+	
9.1.10. Effects on aquatic macrophytes																					+	
9.2. Terrestrial toxicity, initial tests																						
9.2.1. Effects on soil micro-organisms		+	+		+	+	+	+	+	+	+	+		+	+	+		+	+	+	+	
9.2.2. Effects on earthworms or other soil-dwelling non-target invertebrates		+	+		+	+	+	+	+	+	+	+		+	+	+		+	+	+	+	
9.2.3. Acute toxicity to plants		+	+		+	+	+	+	+	+	+	+		+	+	+		+	+	+	+	
9.3. Terrestrial tests, long term		+	+		+	+	+	+	+	+	+	+			+	+		+	+	+	+	
9.3.1. Reproduction study with earthworms or other soil-dwelling non-target invertebrates		+	+		+	+	+	+	+	+	+	+			+	+		+	+	+	+	
9.4. Effects on birds			+											+		+		+		+		
9.5. Effects on arthropods																		+				
9.5.1. Effects on honeybees																		+				
9.5.2. Other non-target terrestrial arthropods, e.g. predators																		+				
10. ENVIRONMENTAL FATE AND BEHAVIOUR																						

[15] Three studies with marine/brackish species are required for specific uses in those PTs which are marked with "+": acute toxicity to fish, to invertebrates and a growth inhibition test on algae

Product-type:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
10.1. Fate and behaviour in water and sediment																						
10.1.3.2. Biodegradation in freshwater			+					+			+						+		+		+	
10.1.3.3. Biodegradation in sea water			+					+			+	+				+	+		+		+	
10.1.3.4. Biodegradation during manure storage			+		+									+	+	+		+	+	+		
10.2. Fate and behaviour in soil																						
10.2.1. Laboratory study on rate and route of degradation including identification of the processes involved and identification of any metabolites and degradation products in one soil type (unless pH dependent route) under appropriate conditions. Laboratory studies on rate of degradation in three additional soil types		(+)	(+)		(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)		(+)	(+)	(+)		(+)	(+)	(+)	(+)	(+)
10.2.4. Adsorption and desorption in at least three soil types and, where relevant, adsorption and desorption of metabolites and degradation products		(+)	(+)		(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)		(+)	(+)	(+)		(+)	(+)	(+)	(+)	(+)

According to the outcome of the risk assessment, further data might be required for the active substance. Thus, not all endpoints of the ADS are assigned to specific PTs/emission pathways.

5.2. Guidance on product-type specific additional data set for biocidal products

Information on the releases following the use of the product is always required and it is a part of the core data set (Chapter III Section 10.1). However, for some PTs additional information on the release after use of the product is needed and therefore further detailed below, depending on the PT.

If a product contains two or more active substances or a substance(s) of concern, or if other ingredients of the product might enhance the bioavailabilty of the active substance, the effects of the product on non-target organisms might be significantly different to those of the active substances alone. In those cases, where a direct release of a product to a given compartment is possible, so that the composition of the product is maintained, additional tests regarding the effects towards non-target organisms performed with the product might be necessary. For the compartments directly exposed, the risk assessment can be performed based on the results of the tests performed with the product.

Please note in addition:

- Other uses might exist which give rise to direct exposure, for which additional tests might also be necessary.
- According to the outcome of the risk assessment further data might be required for the product. Thus, not all endpoints of the ADS are assigned to specific PTs.
- Data on the average amount of the product which may be left in the package to be disposed of should be submitted.

Product-type 1: Human hygiene

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, for the quantification of emission fluxes for human hygiene biocidal products information should be supplied (as far as not covered in BPR Annex III Section 7) on the maximum and average amounts of the product that are applied on one person at a time. For disinfectants in general, information should be supplied on how and in what percentage the active substance, its transformation products or the other ingredients in the product are released from the point treated during use and during washing, etc. (e.g. per unit of surface area per unit of time) by evaporation, dissolving in water or another way. Release rates to be given can be either default estimates or measured.

Product-type 2: Disinfectants and algaecides not intended for direct application to humans or animals

For substances to be used as soil or solid waste disinfectants, direct release to soil is possible. Furthermore, for substances to be used by gassing, fogging, fumigation or aerosol sprays high releases to the atmosphere and subsequent deposition is possible. It is necessary to perform initial terrestrial tests (as referred to in Chapter III Section 9.2) with the product if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product.

In addition, further information on the release due to the use of the product is needed:

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, information should be supplied for disinfectants in general, on how and in what percentage the active substance, its transformation products or the other ingredients in the product are released from the

point treated during use and during washing, etc. (e.g. per unit of surface area per unit of time) by evaporation, dissolving in water or another way. Release rates to be given can be either default estimates or measured.

Product-type 3: Veterinary hygiene

For substances to be used as soil or solid waste disinfectants, direct release to soil is possible. Furthermore, for substances to be used by gassing, fogging, fumigation or aerosol sprays high releases to the atmosphere and subsequent deposition is possible. It is necessary to perform initial terrestrial tests (as referred to in Chapter III Section 9.2) with the product if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product.

For use in poultry farms, where wild birds are attracted, a test with the product with birds is necessary if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product:

9.3 Effects on any other specific, non-target organisms (flora and fauna) believed to be at risk
- Study on 'Effects on birds' according to Chapter II Section 9.4

If the substance is to be used in marine fish nurseries, the aquatic toxicity tests with marine/brackish species also need to be performed with the product if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product:

9.3 Effects on any other specific, non-target organisms (flora and fauna) believed to be at risk
- Tests with fish according to Chapter II Section 9.1.1 or 9.1.6.1, respectively
- Tests with earthworms or other soil-dwelling non-target invertebrates according to Chapter II Section 9.2.2 or 9.3.1, respectively
- Growth inhibition tests on algae according to Chapter II Section 9.1.3.

In addition, further information on the release due to the use of the product is needed:

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, information should be supplied for disinfectants in general, on how and in what percentage the active substance, its transformation products or the other ingredients in the product are released from the point treated during use and during washing, etc. (e.g. per unit of surface area per unit of time) by evaporation, dissolving in water or another way. Release rates to be given can be either default estimates or measured.

Product-type 4: Food and feed area

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, for the quantification of emission fluxes for food and feed area disinfectants information should be supplied on how and in what percentage the active substance, its transformation products or the other ingredients in the product are released from the point treated during use and during subsequent washing, etc. (e.g. per unit of surface area per unit of time) by evaporation, their dissolving in water or another way. The release rates given can be either default estimates or measured.

Product-type 5: Drinking water

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, for the quantification of emission fluxes for drinking water disinfectants information should be supplied on how and in what percentage the active substance, its transformation products or the other

ingredients in the product are released from the drinking water treatment during or after use (e.g. per volume of treated water per unit of time) by evaporation or are dissolved in water or are released in some other way. Release rates to be given can be either default estimates or measured.

Product-type 6: Preservatives for products during storage

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, for the quantification of emission fluxes, for preservatives for products during storage information should be supplied on:

- the binding of the active substance to the material treated,
- on factors influencing binding properties, and
- on how and in what percentage the active substance, its transformation products or the other ingredients in the product are released from the treated material (e.g. per unit of surface area per unit of time) by evaporation, dissolving or any other way.

Release rates to be given can be either default estimates or measured leaching rates.

In case measured leaching rates are provided, please provide them under

10.3 Leaching behaviour
Different leaching rates may be required, for example in relation to leaching from preserved paints or coatings to be used outdoors with a risk of wetting, leaching from preserved paints or coatings when washed indoors or otherwise in contact with water during its service life and volatilisation from preserved paints or coatings in contact with indoor or outdoor air.

Product-type 7: Film preservatives

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, for the quantification of emission fluxes, for film preservatives information should be supplied on:

- the binding of the active substance to the material treated,
- on factors influencing binding properties
- on how and in what percentage the active substance, its transformation products or the other ingredients in the product are released from the treated material (e.g. per unit of surface area per unit of time) by evaporation, dissolving or any other way.

Release rates to be given can be either default estimates or measured leaching rates.

If measured leaching rates are provided, please provide them under:

10.3 Leaching behaviour
Different leaching rates may be required, for example in relation to leaching during the washing of freshly preserved film (e.g. a textile or a film), leaching from a treated film to be placed outdoors with a risk of wetting, leaching from the treated film when washed indoors or otherwise in contact with water during its service life, and volatilisation from the treated film in contact with indoor or outdoor air.

Product-type 8: Wood preservatives

High releases to the terrestrial compartment are possible during storage of freshly treated wood. It is necessary to perform initial terrestrial tests (as referred to in Chapter III Section 9.2) with the product if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product.

If the substance is to be used for wood in hazard class 5 (salt water) defined in the standard EN 335-1 (CEN 1992), the aquatic toxicity tests with marine/brackish species are required with the product as well if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product:

9.3 Effects on any other specific, non-target organisms (flora and fauna) believed to be at risk

- Tests with fish according to Chapter II Section 9.1.1 or 9.1.6.1, respectively
- Tests with earthworms or other soil-dwelling non-target invertebrates according to Chapter II Section 9.2.2 or 9.3.1, respectively
- Growth inhibition tests on algae according to Chapter II Section 9.1.3.

Alternatively to testing the product, it would be possible to test the leachate. No harmonised methods are currently available though, and further discussion regarding the scope of these tests would be necessary.

In addition, further information on the release due to the use of the product is needed:

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, for the quantification of emission fluxes, for wood preservatives information should be supplied on:

- the binding of the active substance to the material treated,
- factors influencing binding properties
- how and in what percentage the active substance, its transformation products or the other ingredients in the product are released from the treated material (e.g. per unit of surface area per unit of time) by evaporation, dissolving or any other way.

Release rates to be given can be either default estimates or measured leaching rates.

If measured leaching rates are provided, please provide them under:

10.3 Leaching behaviour
Different leaching rates may be required in relation to leaching during storage of freshly preserved wood, leaching from wood above ground with risk of wetting, leaching from wood in contact with water, leaching from wood in contact with soil and volatilisation from wood in contact with air.

Product-type 9: Fibre, leather, rubber and polymerised materials preservatives

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, for the quantification of emission fluxes, for material preservatives information should be supplied on:

- the binding of the active substance to the material treated,
- factors influencing binding properties
- how and in what percentage the active substance, its transformation products or the other ingredients in the product are released from the treated material (e.g. per unit of surface area per unit of time) by evaporation, dissolving or any other way.

Release rates to be given can be either default estimates or measured leaching rates.

If measured leaching rates are provided, please provide them under:

10.3 Leaching behaviour
Different leaching rates may be required, for example in relation to leaching during the washing of freshly preserved material (e.g. a textile), leaching from a treated textile or plastic in or above ground outdoors with a risk of wetting, leaching from the treated material when washed or otherwise in contact with water during its service life, and volatilisation from the treated material in contact with indoor or outdoor air.

Product-type 10: Construction material preservatives

For spray application, high releases to the terrestrial compartment are possible. It is necessary to perform initial terrestrial tests (as referred to in Chapter II, Section 9.2 - CDS) with the product if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product.

In addition, further information on the release due to the use of the product is needed:

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, for the quantification of emission fluxes, for material preservatives information should be supplied on:

- the binding of the active substance to the material treated,
- factors influencing binding properties,
- how and in what percentage the active substance, its transformation products or the other ingredients in the product are released from the treated material (e.g. per unit of surface area per unit of time) by evaporation, dissolving or any other way.

Release rates to be given can be either default estimates or measured leaching rates.

If measured leaching rates are provided, please provide them under:

10.3 Leaching behaviour
Different leaching rates may be required, for example in relation to leaching from a treated construction material in or above ground outdoors with a risk of wetting, leaching from the treated material placed indoors and washed or otherwise in contact with water during its service life, and volatilisation from the treated material in contact with indoor or outdoor air.

Product-type 11: Preservatives for liquid-cooling and processing systems

For substances to be used in the cooling systems with an open cooling tower, a high water discharge to air and subsequent deposition onto soil is possible. In these cases, it is necessary to perform initial terrestrial tests (as referred to in Chapter III Section 9.2 - CDS) with the product if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product.

In addition, further information on the release due to the use of the product is needed:

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, indicate for example the measured or estimated extent of release: frequency and intensity (e.g. dose and duration).

Product-type 12: Slimicides

For inland use of drilling and oil recovery preservatives, it is necessary to perform initial terrestrial tests (as referred to in BPR Annex III, point 9.2) with the product if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product.

For offshore use, the aquatic toxicity tests with marine/brackish species need to be performed additionally with the product if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product:

9.3 Effects on any other specific, non-target organisms (flora and fauna) believed to be at risk

- Tests with fish according to Chapter II Section 9.1.1 or 9.1.6.1, respectively
- Tests with earthworms or other soil-dwelling non-target invertebrates according to Chapter II Section 9.2.2 or 9.3.1, respectively
- Growth inhibition tests on algae according to Chapter II Section 9.1.3.

Alternatively to testing the product, it would be possible to test the leachate. No harmonised methods are currently available though, and further discussion regarding the scope of these tests would be necessary.

In addition, further information on the release due to the use of the product is needed:

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, give information for example on the percentage of the active substance or a substance of concern adsorbed to pulp or paper in the manufacturing process. Indicate measured or estimated extent of release: frequency and intensity (e.g. dose and duration).

Product-type 13: Working or cutting fluid preservatives

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, indicate for example the measured or estimated extent of release: frequency and intensity (e.g. dose and duration).

Product-type 14: Rodenticides

If used outside of buildings in the form of baits, granulates or powder, an avian toxicity test (as referred to in Chapter III Section 9.4 (Effects on birds) and as referred to in Chapter III, Section 9.4) is necessary with the product if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product.

Furthermore, in order to assess risks to predators residue data in target organisms concerning the active substance and including toxicologically relevant metabolites would be needed if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product.

In addition, further information on the release due to the use of the product is needed:

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, indicate for example the measured or estimated extent of release: frequency and intensity (e.g. dose and duration). Information should be supplied on the leaching rate of active substances due to weathering of e.g. baits, granules or contact pastes. This can be either default estimates or measured leaching rates.

If measured leaching rates are provided, please provide them under:

10.3 Leaching behaviour.

Product-type 15: Avicides

In order to assess risks to predators residue data in target organisms concerning the active substance and including toxicologically relevant metabolites would be needed if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product.

In addition, further information on the release due to the use of the product is needed:

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, indicate for example the measured or estimated extent of release: frequency and intensity (e.g. dose and duration). Information should be supplied on the leaching rate of active substances due to weathering of e.g. baits, granules or contact pastes. This can be either default estimates or measured leaching rates.

If measured leaching rates are provided, please provide them under:

10.3 Leaching behaviour.

Product-type 16: Molluscicides

For products used outside buildings in contact with soil, release to soil is possible. It is necessary to perform initial terrestrial tests (as referred to in Chapter III Section 9.2) with the product if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product.

If used outside of buildings in the form of baits, granulates or powder, an avian toxicity test (as referred to in Chapter III Section 9.4 (Effects on birds) and as referred to in Chapter III Section 9.4) is necessary with the product if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product.

For molluscicides used in marine waters, the aquatic toxicity tests with marine/brackish species need to be performed with the product as well if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product:

9.3 Effects on any other specific, non-target organisms (flora and fauna) believed to be at risk

- Tests with fish according to Chapter II Section 9.1.1 or 9.1.6.1, respectively
- Tests with earthworms or other soil-dwelling non-target invertebrates according to Chapter II Section 9.2.2 or 9.3.1, respectively
- Growth inhibition tests on algae according to Chapter II Section 9.1.3.

For molluscicides to be used in water, residue studies with the product are necessary if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product:

9.3 Effects on any other specific, non-target organisms (flora and fauna) believed to be at risk

- Tests on bioconcentration in aquatic organisms according to Chapter 9 Section 9.1.4.

Furthermore, possible monitoring data or results of residues studies including toxicologically relevant metabolites, if these cause harmful effects on human health.

In addition, further information on the release due to the use of the product is needed:

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, indicate for example the measured or estimated extent of release: frequency and intensity (e.g. dose and duration). Information should be supplied on the leaching rate of active substances due to weathering of e.g. baits, granules or contact pastes. This can be either default estimates or measured leaching rates.

If measured leaching rates are provided, please provide them under:

10.3 Leaching behaviour.

Product-type 17: Piscicides

For piscicides, the freshwater aquatic toxicity tests (as referred to in Chapter III, Section 9.1) need to be performed with the product as well if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product.

If the substance is to be used in a marine environment, the marine/brackish aquatic toxicity tests need to be performed with the product as well if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product:

9.3 Effects on any other specific, non-target organisms (flora and fauna) believed to be at risk

- Tests with earthworms or other soil-dwelling non-target invertebrates according to Chapter II Section 9.2.2 or 9.3.1, respectively
- Growth inhibition tests on algae according to Chapter II Section 9.1.3

Residue studies with the product are also necessary if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product:

9.3 Effects on any other specific, non-target organisms (flora and fauna) believed to be at risk

- Tests on bioconcentration in aquatic organisms according to Chapter 9 Section 9.1.4

Furthermore, possible monitoring data or results of residues studies including toxicologically relevant metabolites, if these cause harmful effects on human health.

In addition, further information on the release due to the use of the product is needed:

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, indicate for example the measured or estimated extent of release: frequency and intensity (e.g. dose and duration).

Product-type 18 and 19: Insecticides, acaricides and products to control other arthropods and Repellents and attractants

For products used outside buildings as well as products to be used by gassing, fogging or fumigation, release to soil is possible. It is necessary to perform initial terrestrial tests (as referred to in Chapter Section 9.2) with the product if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product.

If used outside of buildings in the form of baits, granulates or powder, an acute avian toxicity test (as provided to in Chapter III Section 9.4.2) is necessary with the product if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product.

Furthermore, a test with bees (as referred to in Chapter III Section 9.5) is necessary if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product.

For products to be used by gassing, fogging or fumigation of a large proportion of a specific habitat type, an assessment of the secondary ecological effect might be necessary:

9.5 Secondary ecological effect e.g. when a large proportion of a specific habitat type is treated

In addition, further information on the release due to the use of the product is needed:

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, indicate for example the measured or estimated extent of release: frequency and intensity (e.g. dose and duration). Information should be supplied on the leaching rate of active substances due to weathering of e.g. baits, granules or contact pastes. This can be either default estimates or measured leaching rates.

If measured leaching rates are provided, please provide them under:

10.3 Leaching behaviour.

If the substance is to be used as a shark repellent, the aquatic toxicity tests with marine/brackish species need to be performed additionally with the product if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product:

9.3 Effects on any other specific, non-target organisms (flora and fauna) believed to be at risk

- Tests with fish according to Chapter II Section 9.1.1 or 9.1.6.1, respectively
- Tests with earthworms or other soil-dwelling non-target invertebrates according to Chapter II Section 9.2.2 or 9.3.1, respectively
- Growth inhibition tests on algae according to Chapter II Section 9.1.3

Product-type 20: Control of other vertebrates

If used outside of buildings in the form of baits, granulates or powder, an avian toxicity test (as provided in Chapter III Section 9.4) is necessary with the product as well if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product.

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, indicate for example the measured or estimated extent of release: frequency and intensity (e.g. dose and duration). Information should be supplied on the leaching rate of active substances due to weathering of e.g. baits, granules or contact pastes. This can be either default estimates or measured leaching rates.

If measured leaching rates are provided, please provide them under:

10.3 Leaching behaviour.

Product-type 21: Antifouling products

The aquatic toxicity tests with marine/brackish species need to be performed additionally with the product if the data on the active substance cannot give sufficient information and if there are indications of risk due to specific properties of the biocidal product:

9.3 Effects on any other specific, non-target organisms (flora and fauna) believed to be at risk

- Tests with fish according to Chapter II Section 9.1.1 or 9.1.6.1, respectively
- Tests with earthworms or other soil-dwelling non-target invertebrates according to Chapter II Section 9.2.2 or 9.3.1, respectively
- Growth inhibition tests on algae according to Chapter II Section 9.1.3

Alternatively to testing the product, it would be possible to test the leachate. No harmonised methods are currently available though, and further discussion regarding the scope of these tests would be necessary.

Residue studies are also necessary:

9.3 Effects on any other specific, non-target organisms (flora and fauna) believed to be at risk

- Tests on bioconcentration in aquatic organisms according to Chapter 9 Section 9.1.4

Furthermore, possible monitoring data or results of residues studies including toxicologically relevant metabolites, if these cause harmful effects on human health.

In addition, further information on the release due to the use of the product is needed:

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, indicate for example the measured or estimated extent of release: frequency and intensity (e.g. dose and duration).

If measured leaching rates are provided, please provide them under:

10.3 Leaching behaviour
Especially for antifouling products in order to quantify emission fluxes, information should be supplied on the average and maximum leaching of the active substance from the film (e.g. per unit of surface area per unit of time). Factors influencing the leaching properties (e.g. time passed after application, temperature, pH, salinity, vessel speed, erosion rate of coating, film thickness) should be named. Release rates to be given can be either default estimates or measured leaching rates.

Product-type 22: Embalming and taxidermist fluids

10.1 Foreseeable routes of entry into the environment on the basis of the use envisaged
In addition to the data to be submitted as core data, information should be supplied for embalming and taxidermist fluids on how and in what percentage the active substance, its transformation products or other ingredients in the product are released from the point during use and during storage of treated material, etc. (e.g. per unit of surface area per unit of time) by evaporation, dissolving in water or another way. Release rates to be given can either default estimates or measured.

VI. Information requirements for substances of concern

The guidance text to be provided in this section is under development and will be made available later on.

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