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Exposure informed testing under REACH



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Abstract

Exposure informed testing under REACH

The level of exposure of humans and organisms in the environment to chemical substances can directly influence the number of tests with experimental animals that are necessary to ensure the adequate safety assessment of those substances. The consequence of this approach is that some tests may be waived if it can be shown that humans or organisms in the environment are either not or only minimally exposed to these substances (Exposure-Based Waiving, EBW). In such cases, fewer experimental animals are needed. In contrast, extra testing can be necessary – and therefore extra experimental animals – when the exposure to such substances is high (Exposure-Based Triggering, EBT).

Extensive knowledge of the level and type of exposure through modelling or monitoring is essential for both EBW and EBT. Such modelling/monitoring applies to all relevant life-cycle stages of a substance, from the production to the waste stage. Only if such knowledge is available can the exposure be assessed to be relevant or not. In this context, the term exposure encompasses the direct exposure of humans to substances at the workplace or via consumer products, the indirect exposure of humans to substances via the environment as well as the exposure of organisms in the environment.

RIVM and the Netherlands Organisation for Applied Scientific Research (TNO) have investigated how EBW and EBT can be used as a determinant in applying testing strategies and how EBW can be used to reduce the number of experimental animals required for the tests. This report is a product of the European Union's Sixth Framework Project OSIRIS (Optimized Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-Test and Test Information). The aim of OSIRIS is to develop testing strategies for application under REACH that will lead to a reduction in the number of animal tests.

The new European Regulation for the Registration, Evaluation, Authorisation and restriction of Chemicals (REACH) requires industry to submit a registration dossier. REACH has established tonnage-dependent testing requirements for industry. Under specific conditions, such as where exposure can be shown to be absent or minimal, REACH allows waiving of the tests.

Key words:

REACH, exposure based waiving, test strategy, alternatives for animal experiments, chemicals

Rapport in het kort

De rol van blootstelling in REACH-teststrategieën

De mate waarin mensen blootstaan aan chemicaliën kan het aantal testen met proefdieren beïnvloeden dat nodig is om de veiligheid van een stof te beoordelen. Dit betekent dat bepaalde onderzoeken niet nodig zijn als mensen of organismen in het milieu niet of nauwelijks aan een stof staan blootgesteld (Exposure Based Waiving, EBW). Hierdoor zijn minder proefdieren nodig. Bij relatief hoge blootstellingen kunnen juist extra testen met proefdieren nodig zijn (Exposure Based Triggering, EBT).

Goede kennis van deze blootstelling via modellering of meting is hiervoor onontbeerlijk, zowel voor EBW als EBT. Dit geldt voor alle relevante stadia in de levenscyclus van een stof, van productie tot de afvalfase. Alleen dan kan gezegd worden of een blootstelling niet of juist wel relevant is. Het gaat om blootstelling van de mens, direct via consumentenproducten of op de werkplek of indirect via het milieu, en om blootstelling van organismen in het milieu.

Het RIVM en TNO hebben onderzocht hoe dit onderdeel van teststrategieën kan worden aangewend om proefdiergebruik te verminderen. Het rapport is een deelproduct van het Europese Zesde Kaderproject OSIRIS (Optimized Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-Test and Test Information). Doel van dit project is om teststrategieën te ontwikkelen voor toepassing onder REACH die het proefdiergebruik kunnen verminderen.

De nieuwe Europese Verordening voor registratie, beoordeling, autorisatie en beperkingen voor chemische stoffen (REACH) verplicht de industrie om een registratiedossier voor haar stoffen in te dienen. De verplichte testen zijn in REACH vastgelegd en afhankelijk van de hoeveelheid stof die op de markt komt. Onder bepaalde voorwaarden, zoals de mate van blootstelling, kan hiervan worden afgeweken.

Trefwoorden:

REACH, exposure based waiving, blootstelling, teststrategie, alternatieven voor dierproeven, chemicaliën

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Summary

This report is one of the products of the EU Sixth Framework project OSIRIS (Optimized Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-Test and Test Information). The aim of OSIRIS is to develop Integrated Testing Strategies (ITS) to be applied under REACH. ITS will make it possible to increase the use of non-testing information for regulatory decision making of chemicals, and to effectively reduce animal testing without increasing the overall uncertainty. Testing strategies will be developed for transparent and scientifically sound human and environmental assessment of chemicals, carried out by regulators and associated institutes and industry. This will allow decision making to be built on information-rich combinations of alternative methods and optimized experimental information.

Exposure is one of the decision elements in ITS. Testing can be waived (EBW = Exposure Based Waiving) or triggered (EBT = Exposure based Triggering) on the basis of exposure considerations. This report aims to describe criteria for exposure informed testing (EBW/EBT) as foreseen in the REACH regulation and to give more detail to the REACH requirements for exposure-based waiving. Starting point is the REACH-text as well as the results of the final guidance developed in REACH Implementation Project (RIP) 3.3 on ITS.

This report analyses EBW and EBT, the conditions for EBW/EBT and how these should be justified in a chemical safety report (at tonnage levels > 10 t/a). This justification can be based on a qualitative argumentation or quantitative argumentation. Qualitative argumentation can be applied when it is obvious that certain exposure pathways are irrelevant, e.g. due to physico-chemical substance properties of a substance. If absence of exposure cannot be argued in a qualitative sense, an exposure assessment and risk characterization based on hazard and exposure may be needed, based on the exposure scenario developed in the Chemical Safety Report.

Extensive and detailed knowledge of exposure throughout the life cycle for human and environmental exposure is essential for exposure based waiving, including occupational exposure, consumer exposure and human exposure via the environment. All stages in the life-cycle of a chemical should be taken into account for a valid justification of waiving.

Significant work on exposure-based waiving and triggering and inclusion of exposure-based waiving in Intelligent Testing Strategies (ITS) has been done in an earlier Reach Implementation Project. However, there are many issues to be resolved, e.g. on definitions and criteria for 'not relevant exposure' and on methods to show that exposures are indeed 'not relevant'.

This report first makes an inventory of waiving options under REACH for human and environmental endpoints and discusses the qualitative and quantitative justifications needed for EBW/EBT. Quantitative justifications depend on the availability of effect levels of no concern such as PNECs (Predicted No-Effect Concentrations), DNELs (Derived No-Effect Levels) and TTCs (Thresholds of Toxicological Concern). The concept of TTC is discussed briefly. Next, examples of EBW/EBT situations and criteria are provided for subsequently environmental exposure, direct exposure of consumers and workers and internal (systemic) human exposure. And finally this report will discuss what this all means for the current exposure assessment methodology.

Abbreviations used

| | |
|-----------------|---|
| ADME | Absorption, Distribution, Metabolism, Excretion |
| C&L | Classification and Labelling |
| CSA | Chemical Safety Assessment |
| CSR | Chemical Safety Report |
| DMEL | Derived Minimal Effect level |
| DNEL | Derived No-Effect level |
| EBT | Exposure Based Triggering |
| EBW | Exposure Based Waiving |
| EMEA | European Medicines Agency |
| ES | Exposure Scenario |
| EUSES | European Union System for the Evaluation of Substances |
| ETCN | Environmental Threshold of No Concern |
| ITS | Integrated Testing Strategy |
| K _{ow} | n-octanol-water partition coefficient |
| kPa | kilopascal |
| MOA | Mode Of Action |
| MW | Molecular Weight |
| μm | micrometer |
| OECD | Organization of Economic Co-operation and Development |
| OSIRIS | Optimized Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-Test and Test Information |
| (Q)SAR | (Quantitative) Structure Activity Relationship |
| PBTK | Physiologically-Based-ToxicoKinetic (Modelling) |
| PBT | Persistent, Bioaccumulative, Toxic substance |
| PNEC | Predicted No-Effect Concentration |
| REACH | Registration, Evaluation, Authorisation and restriction of CHemicals |
| RIP | REACH Implementation Project |
| RIVM | National Institute of Public Health and the Environment |
| RMM | Risk Management Measures |
| STP | Sewage Treatment Plant |
| TG | Test Guideline |
| TGD | Technical Guidance Documents |
| TTC | Threshold of Toxicological Concern |
| vPvB | very Persistent and very Bioaccumulative substance |

1 Introduction

On June 1, 2007, the new European legislation on industrial chemicals, REACH (Registration, Evaluation, Authorization and restriction of Chemicals) entered into force (EC, 2007a; Van Leeuwen et al., 2007a). The purpose of REACH is to ensure a high level of protection of human health and the environment, as well as the free movement of substances, on their own, and in preparations and articles, while enhancing competitiveness and innovation. The consequence of REACH is that in a relative short time period the risk of a large group of chemicals has to be assessed, which implies that also a large amount of information on the fate and effects of chemicals has to become available. In principle, this can be achieved by conducting a large number of human toxicity and ecotoxicity studies as well environmental fate and behaviour studies.

However, not only in the REACH Regulation but also within OECD, there is understanding that for reasons of animal welfare, costs and logistics, it is important to limit the number of tests to be conducted. The REACH Regulation outlines a number of rules for the adaptation of the standard information requirements for specific endpoints (Annexes VII-X). In addition, in Annex XI of REACH, it is specified that the generation of a comprehensive test data set for every chemical will not be needed if these test data can be replaced by alternative data or evidence obtained by the following methods:

- non testing methods:
 - the application of grouping (categories) and read-across
 - computational methods (SARs, QSARs and biokinetic models)
 - thresholds of toxicological concern (TTCs)
 - exposure assessment or exposure-based waiving (and triggering)
- testing methods:
 - *in vitro* tests
 - optimised *in vivo* tests

Since most of these alternative methods can not be used as stand alone, it is necessary to integrate them into a so-called integrated or intelligent testing strategy (ITS) (Combes and Balls, 2003; Bradbury et al., 2004; Vermeire et al., 2007; Van Leeuwen et al., 2007b) In this way, all possible available information on a substance can be optimally used.

REACH Implementation Project (RIP) 3.3 provided guidance on information requirements under REACH and testing strategies for all endpoints (EC, 2007b). Point of departure is the clear obligation under REACH (article 13) to carry out vertebrate testing only as a last resort, thereby placing an obligation on industry and authorities to consider all options before carrying out such testing. Figure 1 shows the General Decision Making Framework developed in RIP 3.3. Figure 2 shows a more detailed illustration of the process to complete the information requirements in the case of inadequate information based on Annex XI.

None of the components in an ITS, e.g. (Q)SAR, *in vitro* testing, *in vivo* testing, exposure modelling, is *a priori* more important than any other, since the ultimate aim is to obtain reliable information on the (toxic) properties of chemicals with minimal use of animals. In principle, the information could be obtained in multiple ways by means of different combinations of the components. However, some ways could be more efficient than others, depending on the underlying rationale of the strategy (e.g. minimizing the over-labelling of chemicals). ITS are hierarchical in nature starting by making maximum use of existing effects and exposure data. Key to the resulting decision schemes is the Weight-Of-Evidence process to be followed which should be as explicit as possible in order to determine the uncertainty in their outcome (Vermeire et al., 2007; EC, 2007b).

This report is written in the context of the EU Sixth Framework Project OSIRIS (Optimized Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-Test and Test Information). The aim of OSIRIS is, further to RIP 3.3, to develop integrated testing strategies fit for REACH that enable to significantly increase the use of non-testing information for regulatory decision making, and thus to minimize the need for animal testing. This report is part of objective 3 of OSIRIS: to develop

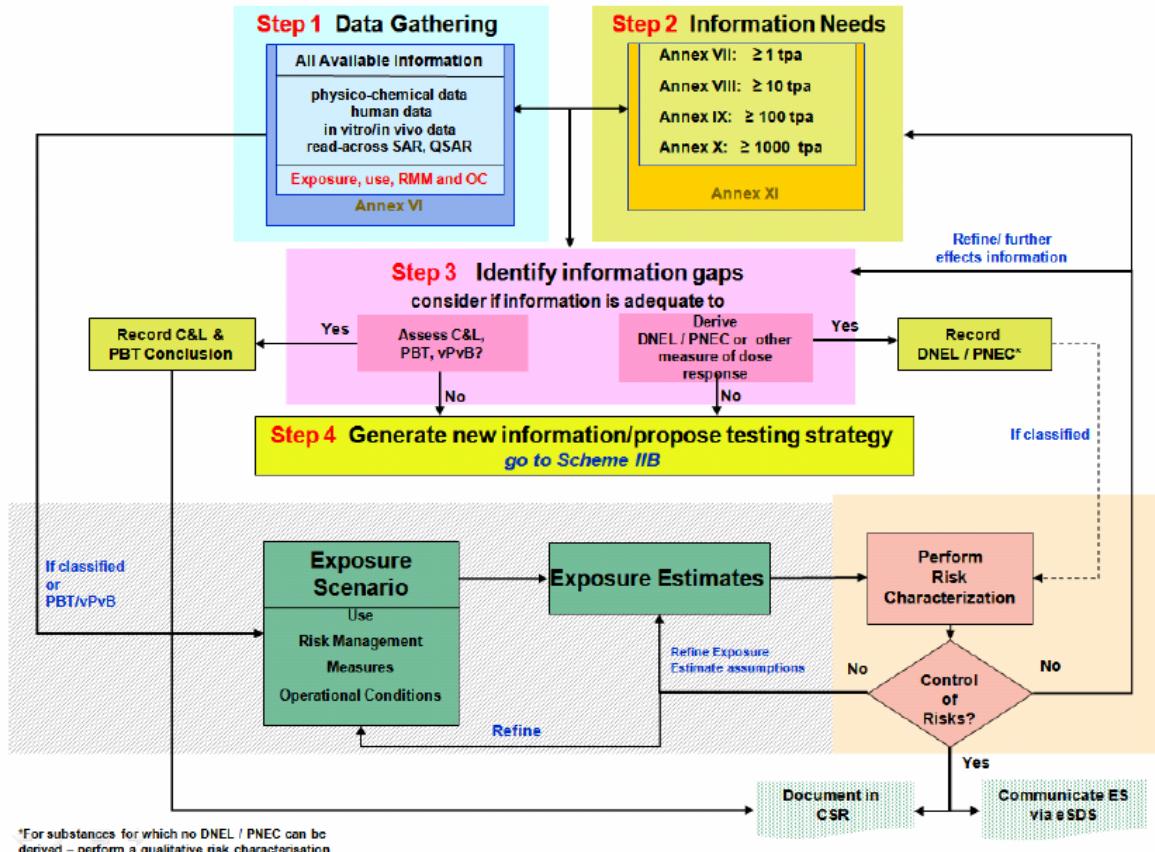


Figure 1: RIP 3.3 General Decision Making Framework. Step 4 is detailed in Figure 2 (EC, 2007b).

criteria for exposure informed testing as foreseen in the REACH regulation, and to refine relevant exposure assessment methods accordingly. Exposure informed testing refers to either waiving of tests based on

an exposure assessment (Exposure Based Waiving, EBW, no 3 in Figure 2) or triggering of testing based on an exposure assessment (Exposure Based Triggering, EBT, e.g. most right arrow in Figure 1). Exposures considered are direct human exposure at the workplace and of consumers and environmental exposure of humans (indirect exposure via the environment) and wildlife, and take into account relevant exposure scenarios including use patterns and conditions of use.

The aim of this OSIRIS subproject is first of all to discuss the principles of EBW or EBT under REACH and to make an inventory of possibilities for EBW/EBT in the REACH Regulation (chapter 2). Next, in chapter 3 it will be investigated what justification is needed for EBW/EBT. Chapter 4 discusses examples of exposure conditions enabling EBW/EBT. This analysis will lead to criteria for exposure assessment methodology which will be discussed in chapter 5.

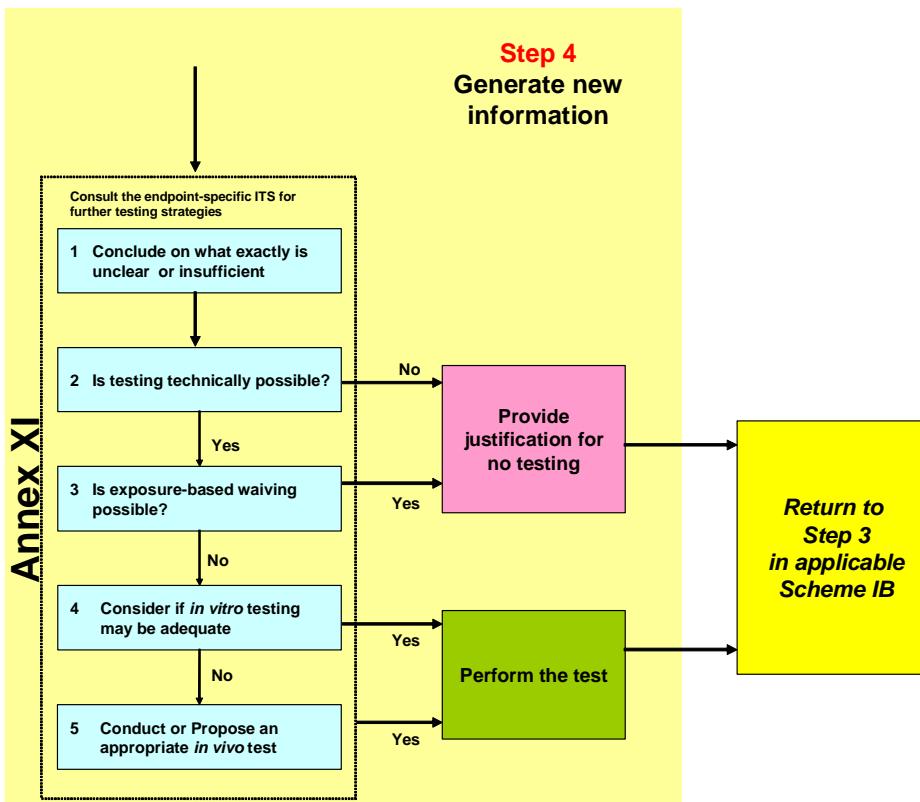


Figure 2: RIP 3.3 General Decision Making Framework Scheme IIB: Step 4 of Figure 1 (EC, 2007b).

2 Inventory of exposure informed testing

2.1 General principles

Exposure informed testing includes both Exposure Based Waiving (EBW) and Exposure Based Triggering (EBT). The principle behind any EBW is that there are situations when human or environmental exposures are so low that there is a very low probability that the acquisition of additional effects information may lead to an improvement in the ability to manage risk. In contrast, EBT refers to situations where human or environmental exposures are considered high enough to justify testing above the requirements laid down in Annexes VI-X.

In the Annexes VII-X of the REACH proposal (EC, 2007a) specific rules are presented when standard information, as specified in Annex VI, may be omitted, triggered, replaced or adapted. No possibilities for EBW exist below a tonnage of 10 tonnes per annum. Therefore, so-called 'column 2' adaptations for EBW/EBT only come into play from Annex VIII. In addition, Annex XI, section 3, presents the possibility of the waiving of certain effects information in Annex VIII, IX and X based on 'the exposure scenario(s) developed in the Chemical Safety Report ('substance-tailored exposure driven testing'). The inventory of 'column 2' options for EBW/EBT in REACH and the RIP 3.3 report is shown in Section 2.2 of this report.

EBW and EBT can best be considered within the context of a risk-based decision making, in order to waive effects information where allowed. Extensive and detailed knowledge of exposure throughout the life cycle for human and environmental exposure is essential for exposure informed testing. Human exposure includes occupational exposure, consumer exposure and human exposure via the environment. All stages in the life-cycle of a chemical should be taken into account for a valid justification of waiving.

The justification for EBW/EBT in a Chemical Safety Report can be based on either a qualitative argumentation or a quantitative argumentation (EC, 2007c).

Qualitative argumentation can be applied when it is obvious that certain exposure pathways are irrelevant, e.g. due to physico-chemical properties of a substance (see section 3). In cases where it is less obvious, a weight of evidence approach may be more appropriate.

If absence of exposure cannot be argued in a qualitative sense, an exposure assessment and risk characterization based on hazard and exposure may be needed, considering the exposure scenario developed in the Chemical Safety Report. The requirements for this are mentioned in chapter 3.

2.2 Inventory

2.2.1 Overview

In summary, the following waiving options exist under REACH:

1. It is always possible to waive in accordance with Annex XI, provided the conditions laid down in Annex XI are met. However, section 3 of Annex XI cannot be applied to waive:
 - information requirements of Annex VII (> 1 tonnes/y)
 - information requirements of all sections of Annex VIII (≥ 10 tonnes per year) except those on repeated dose toxicity (28-days test), section 8.6, and reproductive toxicity (screening), section 8.7
2. It is always possible to waive or trigger in accordance with column 2 of Annexes VII to X, provided the conditions laid down in that column are met. Sections 3.2.2 and 3.2.3 show EBW/EBT options in Annexes VIII to X.

2.2.2 EBW for environmental endpoints

Annex I shows the options for EBW for environmental endpoints in the REACH regulation. No further specifications are given in RIP 3.3.

2.2.3 EBW/EBT for human endpoints

Annex II shows the options for EBW and EBT for human endpoints in the REACH regulation as well as further details from the guidance developed in RIP 3.3.

2.3 Observations

The terminology used in the REACH Regulation for qualitative exposure criteria allowing EBW or EBT is not consistent. The terms used, e.g., ‘relevant exposure can be excluded’, ‘limited exposure’, ‘no (or no significant) exposure’, ‘(un)likely exposure’ can be interpreted in different ways (Bunke et al., 2006). As noted in the introduction, a risk-based approach is therefore advocated based on extensive and detailed knowledge of exposure throughout the life cycle of the chemical and cut-off criteria for adverse effects on human health and the environment.

3 Justification for EBW/EBT

3.1 Introduction

The justification for waiving and triggering should be based on information on hazard, exposure and implementation of risk management measures. One of the main difficulties in EBW is that, in order to decide if exposure is negligible, existing exposure information should be used or it might be needed to collect new or additional exposure information. This then precedes the formal exposure assessment that is part of the Chemical Safety Assessment. This is the trade-off between doing the testing or conduct a qualitative or quantitative exposure assessment and risk characterization. In RIP 3.2-2 a framework was presented, shown in Figure 3, to systematically consider the different options for developing waiving argumentation and documentation (EC, 2007c). The different assessment steps are discussed in the next section.

3.2 Assessment steps

1. Collection of hazard and exposure information

The first step in the assessment starts when the initial hazard information has been collected. All available hazard information should be evaluated before deciding on the waiving possibilities.

The next thing to do is to systematically consider exposure information and routes. It is essential to consider the life-cycle steps of a chemical. Specific exposure routes may be absent and could be a reason for waiving, but exposure may still be an issue during the remainder of its life-cycle. The following life-cycle steps should be considered for occupational, environmental and consumer exposure: production, synthesis, formulation (incorporation of the substance into preparations and articles), industrial, professional and consumer use and resulting service-life and waste stages. In general, exposure information needed for waiving and triggering concerns where the substance is used, how it is used, the intensity of use, predicted exposure and uncertainties:.

2. Definition of waiving conditions and options

The next step is to define which waiving conditions apply (see chapter 1). One should decide if waiving is based on column 2 entries to Annex VIII-X or on Annex XI entries.

If waiving conditions do not apply, the normal procedure is followed in the hazard assessment for the relevant endpoint(s).

3. Justification

Justification is either qualitative or quantitative but always follows a weight of evidence approach.

- Qualitative justification

For all justifications, it is essential that it will be documented on what grounds the waiving is applied (which REACH section), and how it was decided to waive based on exposure information, e.g. can the waiving be documented on qualitative or semi-quantitative arguments (Column 2 adaptations).

Several possible situations are listed in Table 1 that could justify exposure based waiving, due to absence of exposure or exposure that is ‘low, not significant, not-relevant or unlikely’.

Measurements could be used in a semi-quantitative assessment to show that exposure potential is low. Where measured exposure data are included, then as a minimum these need to be described (or referred to the source where this is documented) by the number of samples, frequency of sampling, a description of where/how samples were taken and if samples are representative of normal/unusual operations, limit of detection and basic sample statistics e.g. mean, range, 90th%.

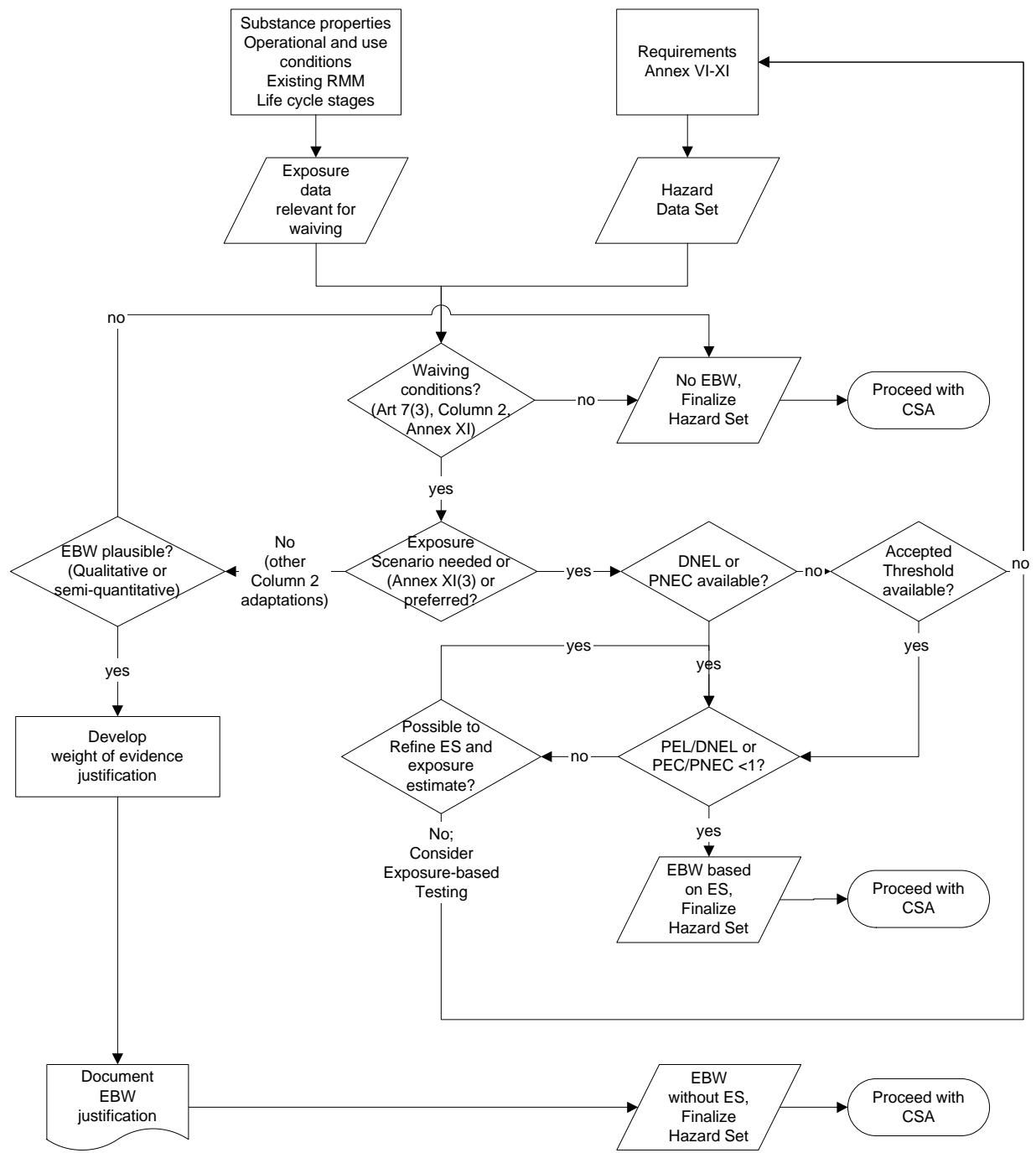


Figure 3: Flow diagram for deciding on EBW or EBT (EC, 2007c)

Table 1: Situations that potentially could lead to EBW (adapted from EC, 2007c)

| Situation for EBW | Explanation |
|--|---|
| Specific use or limited emissions | <p>Certain uses are excluded:</p> <ul style="list-style-type: none"> ○ no consumer application ○ no professional application <p>Emissions to certain environmental compartments are excluded (e.g., air emissions are irrelevant because the substance is a solid and no dusts are formed).</p> <p>Low exposure, due to e.g. small amounts used in total or low emissions/ exposure to the substance, for instance due to a combination of substance properties (low vapour pressure, solids etc.) and ‘negligible emissions’ due to low emission rates and/or tonnage, low frequency of use etc.</p> |
| Specific operational or use conditions | <p>Use is in (semi) closed systems, leading to limited or negligible exposure that should be argued in a qualitative or semi-quantitative way</p> <p>Use in strictly controlled systems with extensive PPE due to the toxicity of the substance</p> |
| Intensity of use (duration, frequency) | <p>Infrequent use due to the function of the substance such as specialty products for highly specific occupational situations with a low frequency and duration</p> |
| Substance properties | <p>Physico-chemical properties of the preparation or article. For instance when a substance is covalently bound to a matrix, e.g. plastic additives)</p> |

▪ Quantitative justification

When a qualitative justification is not preferred, not possible or not allowed, a quantitative justification should be performed based on an exposure assessment and an exposure scenario. Even if this is not required by REACH because the substance is not classified as dangerous or is a PBT/vPvB, an exposure assessment can always be done on a voluntary base including development of an exposure scenario.

An exposure scenario prescribes what a substance is used for, how it is used and under which operational conditions, and what risk management measures are taken to control the exposure of man and the environment. The concise TGD (EC, 2007d) details how an exposure scenario is built and how it is used for the exposure assessment.

The quantitative exposure estimate relevant to the test that is waived will be compared to the derived non-threshold (DMEL) or threshold effect level (PNEC or DNEL) that result from the hazard assessment. If a no-effect level or minimal effect level cannot be derived, it may be possible to use a threshold of toxicological concern (TTC).

If a TTC, accepted within the regulatory framework of REACH, is not available and no DMEL/DNEL or PNEC values can be derived, additional hazard data need to be collected. If a TTC level or DMEL/DNEL or PNEC is available, the exposure assessment will continue with a risk characterization to demonstrate adequately controlled risks. The use of TTCs is discussed within the scope of another OSIRIS Work Package. Since the concept of TTC is crucial for EBW/EBT, the subject will be reviewed briefly in the next section.

3.3 Thresholds of Toxicological Concern (TTC)

3.3.1 Human Threshold of Toxicological Concern

The Threshold of Toxicological Concern (TTC) concept is a pragmatic approach to establish the exposure level below which no adverse effects on human health are expected to occur for chemicals for which toxicity data are not available. It is based on chemical structure and the toxicity data of structurally related chemicals (Kroes et al., 2004). To apply the TTC concept, information about the chemical structure of the substance, but not toxicological information, is prerequisite.

If human exposure to a given substance is below its corresponding TTC value, this may justify EBW. However, also the exposure route should be taken into account when deciding whether EBW is allowed. Thus, ideally a TTC for each exposure route should be available. This is thus far not the case and the TTC concept for human exposure still relies on data for oral toxicity. Incorporation of exposure routes other than the oral route into the TTC concept may be achieved by constructing databases for dermal and inhalation toxicity and deriving exposure route specific TTC values or by applying appropriate route to route extrapolation. Finally, the TTC approach would also benefit from an extension of the existing oral database as it is biased with respect to substances that have no or little first-pass metabolism. This especially holds true for Cramer Class III substances (see below) and may influence the applicability for substances under REACH.

Derivation of TTC for the oral route

Kroes et al., have described a decision tree that can be used to determine which TTC is appropriate to use to analyze the potential risk of exposure to any untested substance (Kroes et al., 2004). Briefly, first non-essential metals, metal containing compounds, proteins, and polyhalogenated-dibenzodioxins and related compounds are excluded from the TTC concept because of their potential risk of accumulation and/or the fact that they were not included in the database used to derive the TTC value. In addition, those substances that are aflatoxin-like, azoxy or N-nitroso-compounds are excluded because of expected highly carcinogenic properties. Importantly, the TTC concept can *only* be used for substance for which it is *excluded* based on their structural properties that they belong to any of the categories mentioned above. Second, based on structural properties of a substance it is decided whether the substance is a potential genotoxic carcinogen. For suspected genotoxic carcinogens a TTC of 0.15 µg/day applies. For substances that are considered not to be genotoxic based on their structural properties, a TTC of 1.5 µg/day can be used to quickly determine whether there is a potential risk given a certain exposure scenario. This TTC however provides a large margin of safety and when it is exceeded this does not necessarily mean that there is any risk to human health. Rather, in this case it should be determined whether the substance belongs to Cramer structural class I, II, or III. This division is based on a decision tree containing 33 questions that mainly concern structural properties of substances, and also take metabolic activation into account. It is designed to classify substances into classes of potential toxicity, I being the lowest and III the highest. Each Cramer structural class has its own TTC (1800, 540, and 90 µg/day for class I-III, respectively). Organophosphates are considered to be a separate group because of their potent neurotoxicity, and were assigned a TTC of 18 µg/day.

Derivation of the TTC for the dermal and inhalation route

Kroes et al. (2007) studied whether the oral TTC values could be applied for the safety evaluation of cosmetic ingredients and impurities. A comparison was made between structural properties of the substances of interest and the substances in the TTC database. In addition, it was determined whether differences in metabolism and absorption after exposure via the dermal route rather than the oral route would lead to major over- or underestimations of toxicity. They concluded that it is scientifically justified to use both the TTC approach and the underlying database for oral toxicity of food chemicals for the safety evaluation of cosmetic ingredients with regard to systemic and not to local effects. For exposure assessment following dermal exposure it was suggested to incorporate default adjustment factors for dermal absorption and intermittent exposure (Kroes et al., 2007). With respect to exposure

via inhalation, one abstract by Ford et al. describes a study in which a TTC approach was used for the evaluation of tobacco additives (Ford et al., 2006). Inhalation NOAELs for approximately 350 chemicals were collected and divided according to the Cramer structural classes. A good correlation between the oral database and the inhalation database was found only for chemicals that did not cause toxic effects at the point of entry. Since this information was based on text from an abstract only, more information is needed on the value of a possible TTC to be used for the inhalation route. This was also concluded by Rennen et al. (2004). Moreover, for the assessment of local effects (both dermal and via inhalation) more information is needed with regard to the derivation of a TTC.

Another point to take into consideration is the use of *endpoint* specific TTC values rather than the TTC values for all types of toxic endpoints that are used in the existing TTC approach. In this respect, a number of endpoints (neurotoxicity, immunotoxicity, developmental toxicity, and reproductive toxicity) was considered to be of special concern and were therefore evaluated separately (Kroes et al., 2004). The cumulative distribution of endpoint specific NOELs was similar to the cumulative distribution of non-specific NOELs, with the exception of the NOELs for neurotoxicity. However, the latter could be attributed to organophosphates alone, which were therefore assigned a separate TTC value. It was not considered necessary to develop endpoint-specific TTC values.

Finally, it should be taken into account that the TTC is based on an assumed body weight of 60 kg and may therefore not be directly applicable as such if a substance is specifically intended to be used by children. More information is needed with a focus on effects in children.

3.3.2 Environmental Threshold of No Concern

Two different approaches have been used when deriving a TTC for the environment and reviewed by TemaNord (2005):

1. The *action-limit* proposed by EMEA/CPMP (2001).
2. The Environmental Threshold of No Concern (ETNC) proposed by ECETOC (2004) and De Wolf et al. (2005).

Both these approaches are restricted to the pelagic freshwater compartment.

The first of these TTC-approaches, i.e. the *action-limit*, originates from a draft on environmental risk assessment of human pharmaceuticals (EMEA/CPMP, 2001), describing a tiered risk assessment process. This action limit is based on an aquatic concentration below which it was concluded that no ecotoxicity data on drugs for relevant standard test organisms were reported (US FDA, 1996). This concentration was further divided by an assessment factor of 100 to obtain the action limit. The validity of this approach was questioned (CSTEE, 2001) since pharmaceuticals with lower effect concentrations were found and because of the focus on acute toxicity.

A different TTC-approach was applied deriving an ETNC for the pelagic freshwater compartment, i.e. ETNC_{aqueous} (ECETOC, 2004; De Wolf et al., 2005). This approach was based on existing toxicological databases and substance hazard assessments for organisms in the freshwater environment, and a categorization of chemicals into four different modes of action (MoA) according to the system by Verhaar et al. (1992). The stratified data was fitted to a lognormal distribution from which a fifth percentile, with a 50% confidence interval, was determined. This value was then divided by an assessment factor, ranging from 1 to 1000 depending on the data to obtain the ETNC_{aqueous}. The four different modes of action used were according to the system by Verhaar et al. (1992):

- MoA1 = inert chemicals (baseline toxicity, narcosis)
- MoA2 = less inert chemicals (acting by polar narcosis)
- MoA3 = reactive chemicals (react unselectively with certain chemical structures in biomolecules)
- MoA4 = specifically acting chemicals (specific or receptor toxicity).

The authors proposed an overall value of 0.1 µg/L for MoA1-3. The authors considered that a broad application of the ETNC_{aqueous} concept also needed to cover MoA4 and that the resulting ETNC_{aqueous} likely would have to be much lower. The authors (De Wolf et al., 2005) suggest that the ETNC_{aqueous} only should be used as a first tier of assessment, in the absence of any effect data.

Criticisms towards using this ETNC aquatic (TemaNord, 2005):

- The TTC approach is developed only for direct effects on the pelagic freshwater ecosystem and not effects due to bioaccumulation, or accumulation in other compartments.
- The concept does not cover metals, other inorganic compounds, or ionisable organic compounds.
- The concept only covers aquatic organisms. The use of this ETCN for deriving a sediment ETCN by equilibrium partitioning is questionable.
- The use of the threshold of no concern, as compared to experimental data, implies a higher risk of not considering the toxicity of degradation product(s)/metabolite(s), which may be unfortunate if they are more toxic than the parent compound.
- When using the ETNC concept, substances that are toxic at very low concentrations may slip through, i.e. those with an effect concentration below the 5th percentile.
- If the ETCN-concept is to be used, should one or several threshold values be used? The use of several thresholds increases dependence on the categorization system. The use of only one threshold value appears to be the most transparent and conservative approach and this then should be based on the threshold value on chronic toxicity data for the most toxic chemicals, i.e. those categorized as having a specific mode of toxic action (MOA4).

4 Examples

4.1 General introduction

The following lists situations in which EBW and EBT are an issue without suggesting that in all these cases EBW is justified. In many cases further criteria need to be developed for justification. Examples are, among others, taken from RIP 3.2-1 and RIP 3.2-2 documentation (EC, 2007b, c and d) and Bunke et al. (2006).

It should be noted, that, for each use of a chemical, EBW will have to apply to all ecosystems or target populations (consumers, workers, humans exposed via the environment), and life cycle stages (production, formulation, professional and consumer use, service life, waste treatment) before it can be decided that tests can be waived. For instance, a 90-days oral test can be waived in view of absence of exposure for workers and consumers, but may still be required in view of environmental exposure of humans. Waiving should also cover uses further down the supply chain, e.g. in preparations.

Conversely, a test can be triggered based on an assessment of only one life cycle stage. Aggregation, across routes, tasks and uses, may also need to be taken into account to assess exposure.

4.2 Environmental exposure

4.2.1 Specific application of EBW

Substance properties

Substances may show properties which will render releases to the environment unlikely and will influence distribution in the environment. Examples are substances which:

- react away during manufacturing (e.g. monomers, intermediates);
- react away under moist conditions;
- are bound covalently to a matrix during manufacturing (e.g., monomers), formulation (e.g. plastics additives) or use (e.g., pigments or dyes in plastic or fibers, plasticizers in plastics, additives such as catalysts in coating materials). Note that in these cases the substance may be released again at waste treatment;
- exhibit low fugacity due to low vapour pressure and dustiness;
- exhibit high volatility and react or degrade rapidly in air.

Other examples relate to substances that show properties that will render releases to a specific compartment unlikely and may therefore induce EBW for these compartments. For instance, releases to soil will be virtually absent for:

- very water soluble chemicals released to water (note this may change if surface water is used for irrigation purposes);
- rapidly hydrolysing chemicals released to water.

These examples are open to interpretation. A Weight of Evidence procedure is needed to evaluate these together with releases, operational conditions and risk management measures (see next paragraphs).

Releases

The use pattern of a substance is often more appropriate to assess emission and exposure than tonnage information of a substance. Limited tonnages therefore often do not provide sufficient grounds for EBW. A limited tonnage produced or processed at one location may still give rise to high local releases. The use of chemicals and resulting releases can be described by its use and release pattern and operational conditions as described in the REACH Exposure Scenario (ES). A substance can be emitted during its various life cycle stages production, formulation, professional and consumer use, service life and waste treatment. The release rate depends on substance properties like volatility and solubility, on applied processes, use frequency and duration, equipment and risk management measures, the technical

function of the substance, and the industrial area where the substance is applied. Depending on the combinations of these elements releases are more or less likely to be expected: some combinations may not occur at all or may not be relevant with respect to the release to certain environmental compartments. The identification of these combinations can be a first step in a (qualitative) EBW approach (see also chapter 3). These combinations of elements of the use and release pattern of a substance may be identified from the release tables and emission scenario documents in the current risk assessment guidance (EUSES/TGD, EC 2003).

Operational conditions and RMMs

Operational conditions and RMMs as described in the ES may be such that releases to all or specific environmental compartments will be low. An obvious example is a closed system with only occasional sampling and maintenance and no further breach. Additional information on emissions (on exhaust air, waste water, cleaning processes, etc.) is necessary, in order to decide finally about waiving. Another example is a chemical with a release pattern that gives rise to transient exposure of the aquatic compartment. Bioaccumulation requires time. An organism which is only briefly exposed to a bioaccumulative chemical may not bioaccumulate it since the window of opportunity is simply too short. Therefore, any situation that involves transient exposure of the aquatic compartment would also seem to be grounds for EBW of this test. However, some chemicals may have such long elimination half-lives that accumulation will also occur in case of discontinuous exposures.

4.2.2 Specific application of EBT

Situations where environmental exposures are considered high enough to justify testing above the requirements laid down in Annexes VI-X are not easy to describe specifically. One general example is provided by uses with wide dispersive – uncontrolled - use of chemicals such as constituents of detergents, cosmetics, disinfectants, household paints, human and veterinary drugs. Whether EBT applies will further depend on the physico-chemical properties of these chemicals and their release rates.

Chemicals, identified as potential PBTs or vPvBs will trigger further testing under REACH.

4.3 Human exposure

4.3.1 General considerations

- Exposure based waiving (EBW) or triggering (EBT) of testing of a certain substance is strictly based on the *exposure* of humans to this substance. Substance specific properties only come into play for as far as they are relevant for the emission of the substance, and hence for the potential human exposure. As the decision to apply EBW or EBT may depend on the toxic potency of the substance, in certain cases also the hazard of the substance should be taken into account and an exposure assessment is needed. Thus hazard of a substance can be used, or needed, to justify EBW, however, only as an addition to and in combination with the exposure scenario. Substance properties that contribute to the potential absorption level of the substance are not taken into account as this aspect of EBW is part of work package 3.3 (internal exposure).
- In REACH several terms are used to indicate levels of human exposure that are considered to justify EBW, such as limited / no / no significant / low exposure. Until now, it is not clear what the difference between these different terms is. To avoid any confusion caused by the random use of these terms, in this paragraph we will refer to the exposure level below which we consider EBW appropriate as the ‘no further action level’. EBW can be applied when it is concluded that human exposure is below ‘no further action levels’. In practice, this level will be determined using a TTC concept taking into account exposure route and/or toxicological endpoint, or can be deduced from the difference (margin of safety) between a DNEL as established from those studies and data that are already available on exposure. In a TTC concept there can be different TTCS for workers than for consumers. Workers are generally healthy adults with an exposure at work of up to not much more than 50 hours per week, while consumers may be very young or old, unhealthy and exposure may occur in some situations 24 hours per day and/or 7 days a week. Alternatively, when there is considerable concern regarding human exposure, EBT should be applied.
- Aspects of the exposure scenario that should be taken into account to determine whether EBW or EBT can be applied are: exposure route, exposure frequency, exposure duration, conditions of use, risk management measures, and the nature and extent of substance emission. According to REACH the exposure scenario of a manufacturer must address the manufacture of a substance and all the identified uses whereas an importer must only address all identified uses. It is not required by REACH to incorporate the uses described in other registrations of the substance. As a consequence, EBW or EBT will be solely based on exposure scenarios of individual manufacturers and importers and might not encompass all uses and possibilities of exposure to a substance.
- Some ways of exposure are considered non-relevant in this scope and will not be taken into account when determining whether or not to apply EBW or EBT. Non-relevant exposure in this scope is defined as exposure that is not the result of the use of a product in a product chain.¹ Examples of exposures that are non-relevant in the scope of EBW and EBT are the exposure to substances (such as acrylamide, PAH) that are formed in cigarette smoke, exposures that result from the use of other substances in which the assessed substance is a contamination according to the definitions of REACH or exposures that result from natural sources, such as substances in soil dust, substances (e.g. fragrances) naturally emitted by plants, etc. Exposures due to accidents are also non-relevant, as far as the accidents are indeed (very) infrequent and not some kind of recurrent incidents that apparently are part of the normal exposure situation.
- When exposure routes can be excluded this may be reason to waive further testing of substances. In accordance with Annex XI section 3 EBW is applicable to repeated dose toxicity studies, sub-chronic toxicity studies and reproduction toxicity studies. In all cases REACH indicates that if EBW is not applied, these studies should be performed for the *most relevant* route of exposure. Identification of this most relevant route of exposure should be based on the exposure scenario. For instance, in theory the most relevant route of a substance may be inhalation although it can also be absorbed via the skin. When the formulation of this substance prevents inhalation, the dermal rather than the inhalation route should be considered the most relevant route of exposure.

¹ Please be aware that this is not intended to define the term ‘no relevant exposure’ as it is used in REACH.

- The justification for EBW can be based on a qualitative argumentation or quantitative argumentation. Qualitative argumentation can be applied when it is obvious that certain exposure pathways are irrelevant, *e.g.* due to physical-chemical substance properties of a substance or as a result of product-related RMMs preventing exposure. In cases where it is less obvious, a weight of evidence approach may be more appropriate. If absence of exposure cannot be argued in a qualitative sense, an exposure assessment and risk characterization based on hazard and exposure may be needed, based on the exposure scenario developed in the Chemical Safety Report. Justification for EBT can be based on qualitative argumentation showing that the level of human exposure is of considerable concern and warrants the gathering of more hazard data through further testing.

4.3.2 Specific applications of EBW

EBW can be applied based on Column 2 of Annex VII-X, which lists specific rules according to which the required standard information may be omitted, replaced by other information, provided at a different stage or adapted in another way (see paragraph 2.2.3). Specifically, EBW based on column 2 is either based on the implementation of appropriate risk management measures for genotoxic or mutagenic substances (in the case of reproductive toxicity) or on the exclusion of exposure routes (in the case of acute toxicity, second route). In addition, the required standard information set out in Annex VIII-X may be adapted according to the general rules contained in Annex XI, section 3: Substance-tailored exposure-driven testing, which states that testing in accordance with sections 8.6 (Repeated dose toxicity and sub-chronic toxicity) and 8.7 (Reproductive toxicity) may be omitted. The justification shall be based on the exposure scenario and/or an exposure assessment. This chapter lists examples of specific situations in which EBW may be an issue, without suggesting that in all these cases EBW is justified. In many cases further criteria need to be developed for justification. Examples are taken from RIP 3.2-1 and RIP 3.2-2 documentation and from Bunke et al. (2006). As indicated in Figure 4, the aspects in the exposure scenario that may justify EBW can broadly be divided in four, sometimes interrelated, clusters and they will be discussed accordingly.

4.3.2.1 Low concentration of substances in preparations

Article 14 of REACH indicates that no chemical safety assessment needs to be performed for a substance which is present in a preparation if the concentration of the substance in the preparation is less than the lowest of any of the concentrations indicated below. It should be noted that, as the regulations mentioned are incorporated in REACH, it is not part of EBW.

- the applicable concentrations defined in the table of Article 3(3) of Directive 1999/45/EC;
- the concentration limits given in Part B of Annex II to Directive 1999/45/EC;
- the concentration limits given in Part B of Annex III to Directive 1999/45/EC;
- the concentration limits given in Annex I to Directive 67/548/EEC;
- the concentration limits given in an agreed entry in the classification and labelling inventory established under Title XI of this Regulation;
- 0.1 % weight by weight (w/w), if the substance meets the criteria in Annex XIII of this Regulation.

For substances that do not fulfil any of the above given requirements, EBW based on low concentration in preparations may be applied in accordance with Annex XI. As REACH implicitly states that no significant health risk exists when the limits given above are met, for gaseous preparations a concentration of 0.02% volume by volume and for other preparations a concentration of 0.1% weight by weight seems reasonable as cut-off level for EBW. These are the lowest concentrations in the Regulation requiring a Chemical Safety Assessment. It should be noted, however, that in addition to the concentration of a substance in a preparation, also the amount used is an important parameter. Therefore, for large amounts used during a (working) day EBW based on these concentrations may not be scientifically justified.

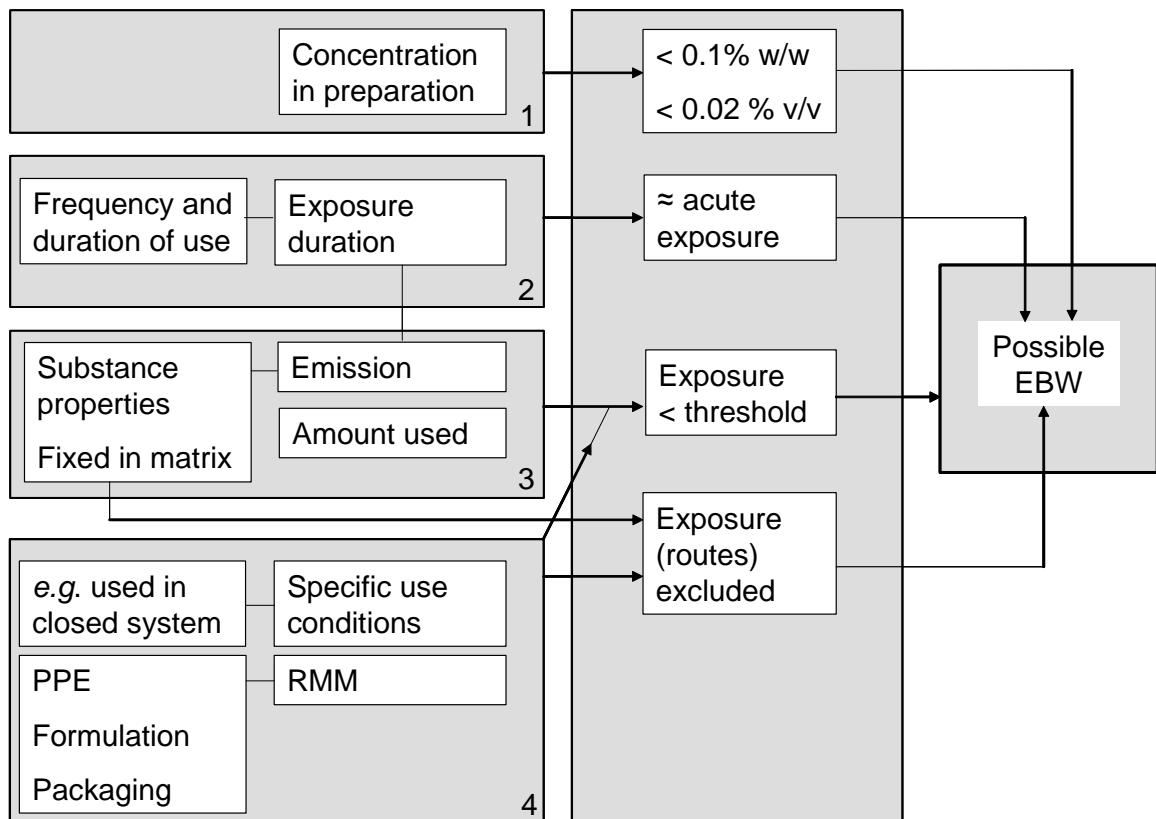


Figure 4: Justification of EBW in the Exposure Scenario

For consumers, exposure to substances that are present in low concentrations in a preparation or are reacted away during its manufacture may clearly be below the ‘no further action level’ and EBW may therefore be allowed. However, for worker exposure this may be more complicated as somebody somewhere has to start the manufacture and may thus be exposed to the substance. Therefore EBW of testing required for worker exposure requires additional information on the use of, and possible worker exposure to the substance during the whole manufacturing process and can not be solely based on the fact that substances are reacted away during manufacture or present in low concentrations in a preparation.

4.3.2.2 Intermediates

When a substance is an intermediate, it can be assumed that it is (nearly) completely reacted away during the manufacturing of preparations or articles. For *preparations*, this can be compared to the waiving of safety assessments for substances that are present in preparations below a particular concentration hence the same criteria can be used to apply EBW. Ideally, sound chemical analysis should be provided to support the assumption that the substance is reacted away during manufacture and to estimate the potential residue concentration in the product. However, a more pragmatic approach could be to work from the default assumption that an intermediate is no longer present in concentrations relevant for exposure after reaction, unless information is available to contradict this default assumption.

4.3.2.3 Exposure is limited to acute exposure

The infrequent use of substances may imply that long-term exposure can be excluded and can therefore justify EBW of repeated dose toxicity studies and sub-chronic toxicity studies in accordance with Annex XI. As all information about the potential toxicity of the substance in this case relies on the acute toxicity studies that are required under REACH, infrequent use should mimic acute exposure to justify EBW. To meet this criterion, use should be both infrequent and not occur consecutively on a

large number of days, e.g. no more than a few days in a row, and on average no more than a few times a year to ensure that exposure remains below the ‘no further action level’. The exact boundary between ‘frequent’ and ‘infrequent’ is not easy to establish. Some guidance can be given for possibly waiving testing effects after repeated exposure:

- ‘once in a lifetime’ exposure is infrequent
- ‘one to five days per year’ exposure is also infrequent
- ‘one day every two weeks’ is not infrequent
- exposure that is ‘daily for a month once in a lifetime’ is not infrequent
- ‘daily’ exposure is not infrequent

Everything between ‘one to five days per year’ and ‘one day every two weeks’ is a grey area and could be assessed on a case by case basis, taking into account other aspects of the exposure scenario as well. In addition, it should be noted that a single *use* can cause long-lasting exposure and can therefore not be regarded as a single *exposure*. EBW based on infrequent use is therefore only applicable to products of which substance emission is of short duration e.g. no more than a few hours. Thus, infrequent use on its own is not sufficient to justify EBW, but should be supported by information on the duration of use and emission of the substance and toxicokinetic data such as half-lives.

Similarly to repeated dose toxicity studies and sub-chronic toxicity studies, reproduction toxicity studies can be waived based on infrequent consumer and worker use in combination with information about duration of use and emission. However, during critical time frames of embryonic development embryotoxic and teratogenic effects may occur after a single exposure to embryotoxic substances. When no information about the potential embryotoxic properties of these substances after acute exposure is available, EBW should be based on exposure levels as compared to a relevant threshold for ‘no further action’ and not solely on the fact that a substance is used infrequently.

4.3.2.4 Amount of substance used and/or substance emission is low

Limited amounts used

- In certain cases EBW may be applicable for substances that are used in limited amounts or low concentrations per day. To justify EBW on this ground, the exposure levels resulting from the use of a substance should remain below a certain ‘no further action’ level. As the potential risk of the exposure to a substance, even when its use is limited, depends on its toxic potency, this level should be based on both exposure to and toxicological properties of the substance. To allow rapid screening, an approach similar to the ECETOC targeted risk assessment was proposed. In accordance with their risk potency, substances can be divided in categories for each of which a threshold is given below which exposure is considered to be below the ‘no further action’ level. The estimated exposure to a substance can be compared to the reference value of the appropriate category to determine whether EBW is applicable. This method should be regarded as a rapid screening method and be based on a worst-case estimation of the daily exposure. When this first screening results in an exceeding of the cut-off level, EBW can not be solely based on the fact that a substance is used in limited amounts per day, but also other factors of the exposure scenario such as specific use conditions or risk management measures should be taken into account. To apply the above described approach, substances should be divided into categories based on their risk potency.

For each category and exposure route a cut-off level can be determined below which consumer and worker exposure is considered to be below the ‘no further action level’ and EBW of repeated dose toxicity studies can be applied. Alternatively a cut-off level per exposure route, encompassing all toxic effects, may be determined using the TTC approach, or can be deduced from the difference (margin of safety) between DNEL and exposure. For substances that show accumulation EBW should only be applied if the accumulated exposure after the number of exposure events that is expected, based on the exposure frequency, is still below the cut-off level. In evaluation of such situations (such as in the PBT assessment) account should be taken of toxicokinetic aspects of the substance and its metabolites.

In the specific case where a substance has no consumer application and is not used in any consumer products, the amount used by consumers is clearly limited. However, to apply EBW, exposure to workers should also remain below the cut-off level. In addition, to rule out consumer exposure, detailed

information on the applications of the substance is needed, as well as information about the possible availability of the substance to the consumer. For instance substances may be intended for professional use, but can be purchased by consumers wholesale.

Low emission and/or exposure due to substance properties

The following substance properties may contribute to low emission and/or exposure:

- Dermal exposure is not relevant when the substance is a gas or a high volatility liquid with short duration of exposure (except when data show relatively high dermal absorption from the vapour or gas phase). The TGD contains an equation to calculate evaporation from the skin. A criterion could be:
 - full evaporation of high levels of contamination can be expected in a matter of minutes (say < 10 minutes), **and**
 - duration of exposure is not more than 10 minutes consecutively and frequency not more than four times per day.

With the equation provided in the TGD and exposure estimates for high exposure tasks, this can be further specified towards the vapour pressure of the substance that will ensure sufficiently quick full evaporation.

- Emission of vapour is considered to be negligible in case of solid substances with a vapour pressure smaller than 1 Pa (at process temperature) and liquids with a vapour pressure smaller than 0.1 Pa (at process temperature) (Bunke et al., 2006). Further testing of substances and preparation of solids and liquids that fit these criteria may thus be subject to EBW.
- Substance properties of liquids that minimize aerosol formation may ensure low emission via the air and hence limited user exposure, which may be reason for EBW. As particle size influences to what extent inhalation occurs, the size of potential aerosols formed is also of importance in this matter.
- In case of solid substances, emission of inhalable dust is considered to be negligible for solids in the form of abrasion-free pellets/ granules. A possible criterion could be that all particles of the original substance should be larger than 100 µm and there should be pertinent information that handling and storage of the substance does not significantly change the particle size distribution towards lower particles.

It should be noted that none of these substance properties on its own is sufficient to assume that human exposure is indeed below a ‘no further action level’ because they do not encompass all possible exposure routes. For instance, exposure via inhalation may be excluded due to properties of a liquid or solid substance. However, when besides the inhalation route the dermal route is also a relevant route of exposure, this can not be used as basis for EBW. In such cases other aspects of the exposure scenario should also be taken into account to determine whether exposure is below the ‘no further action’ level.

Low emission due to fixation in a matrix

As exposure to substances that are fixed in a matrix, e.g. plastic additives, is likely to be limited, this may be reason to apply EBW. The matrix should prevent substance leaching to such an extent that it can reasonably be assumed that exposure to the substance is below the ‘no further action level’ and EBW can be applied. Human exposure via leaching of the substance from the matrix can be compared to a relevant TTC endpoint in order to determine whether EBW is appropriate. Whether substances are firmly fixed in the matrix should be shown in migration studies taking into account the individual usage conditions or comparable information. For instance, inhalation exposure to vapour or dust is not relevant for non-volatiles that are dissolved or dispersed in a liquid (or e.g. an emulsion). However, in case of spraying exposure to aerosols containing the dissolved or dispersed non-volatile is probably relevant. Finally, the exposure of workers during the production of the matrix should also be below the ‘no further action’ level to allow EBW.

4.3.2.5 Specific use conditions and risk management measures

As discussed below, specific use conditions and RMM could justify EBW because they might either reduce the exposure levels or exclude exposure routes. The latter may be reason for EBW provided that no other relevant exposure routes require testing under REACH.

Specific use conditions

In case of consumers, EBW based on specific use conditions of a product may be applicable, for instance, for products that are only intended for outside use. It should be taken into account that consumers do not necessarily comply with the advised or indicated conditions. For instance, suppliers may urge consumers to use a product only in well ventilated areas but they cannot prevent them not doing so. Therefore, to use this aspect of consumer use to justify EBW, it is necessary to provide sound argumentation that the assumption that consumers will comply with specific use conditions is reasonable. In addition, it should be shown that the specific use conditions minimize the contact potential and will result in exposure levels below the 'no further action level' to justify EBW.

In case of workers, assumption of compliance to specific use conditions can be reasonable, but may in practice depend on the type of worker population involved. In addition, these conditions should apply through the chain and should also be applicable for downstream users. In large scale industry, the compliance with use conditions often is monitored by management, specifically if the industry is aware of major risks. In small scale industries or professional use, or in industries that do not have awareness of major risks in their industry, the monitoring of compliance could be less well organized. However, under REACH operational conditions and risk management measures can be prescribed in the Exposure Scenario and it should be assumed that there is compliance with the Exposure Scenario in the work situation. Thus, when it is shown that the specific use conditions results in exposure below the 'no further action level' this could justify EBW.

The use of substance in closed systems is a realistic situation in case of workers in several industries. When a substance is solely used in a closed system, and occasional exposure is restricted to maintenance or sampling tasks and the system containing the substance is not breached, e.g. for quality control sampling or for removal/disposal, EBW may be applicable. However, closed systems are hardly ever really closed. Seams of connections may leak minimal amounts of product. In these cases the substance properties are also relevant to assess whether closed systems are sufficient reason to waive further testing. For very hazardous gases (e.g. butadiene, which is a genotoxic carcinogen) and very high volatility liquids (e.g. HF, which is a severe acutely toxic substance) exposure levels in much closed industrial settings indicate that the combination of high hazard and high volatility is not suited for EBW. Because the hazard is not fully known when EBW is an issue, a criterion of low volatility could be used in combination with criteria for 'closed system' to argue that EBW is possible. Criteria for 'closed system' or 'rigorous containment' are also needed for evaluating whether a substance can be registered as (transported) intermediate. Similar criteria can be used for EBW. EBW based on the use of a substance exclusively in a closed system is probably only applicable for workers, for consumers it is hard to imagine preparations that are used in (sufficiently) closed systems that may be subject to EBW of further testing.

Risk management measures

- Type of formulation

The formulation of a product may in some cases limit the contact potential of a substance and thereby consumer or worker exposure. Although in case of gaseous substances contact potential can not be reduced by formulation of the product and no EBW can be applied based on the formulation, for solids it may be achieved in the following situations:

- Solid substances, preparations or articles may consist of hazardous substances covered with a more or less impervious coating that is not hazardous. When there is only skin contact with these products there is no, or very minimal actual contact with the hazardous substance. Of course, the product should enable the encapsulated substances to perform their required function in the relevant processes.
- In case of powders both dermal exposure and exposure via inhalation can be reduced by compression of the powder into a more dense form. However, dermal exposure can not be excluded even when the powder is compressed and substances that are potentially absorbed via the skin or orally via hand-mouth contact can therefore not be waived from further testing in repeated dose toxicity and reproduction toxicity studies. When the powder does not show any dermal absorption, its formulation into a more dense form justifies EBW, provided that the dense form is not easily reduced to powder and potential inhalation can be excluded. If aerosol formation with the dense

powder form occurs, the particles sizes should be large enough to prevent inhalation exposure, e.g. via criteria as mentioned earlier. Very large particles do not stay airborne and inhalation exposure to relevant concentrations is not possible.

- Packaging designed to limit inappropriate exposure

The packaging of substances may in certain cases limit consumer and worker exposure and thereby justify EBW. For instance in the rubber industry, solids can be packaged in bags that do not need to be opened, but can be added to the production system in the bag. The bag material is either destroyed (e.g. burned) during the process or incorporated in the end product (e.g. as a kind of filler material). Another example is a specific packaging for two component adhesives that ensures that the correct amounts of each component are mixed already in the spout, thereby preventing use of excessive amounts of one substance and/or the need to handle residual amounts of one of the substances as waste material.

Especially in the case of consumers, proper use should be a reasonable assumption. Low exposure and exclusion of certain exposure routes may help to justify EBW when the exposure of both workers and consumers to these substances is sufficiently reduced.

- Substances used in the workplace by well-trained people, clear protocols, using suitable PPE

In some cases substances are used in workplaces in strictly controlled system with extensive PPE due to the known (acute) toxicity of the substance or due to the hazards of other substances handled in the same process. In such cases (e.g. in parts of the chemical industry) it can be shown quantitatively or qualitatively that shift average exposures over long periods are very low, possibly low enough to justify EBW. Adequate justification is essential.

The use of PPE alone is not considered to prevent exposure sufficiently, i.e. PPE are not a justification for waiving. PPE is an additional criterion together with the other criteria. When PPE is used in the justification for waiving the following requirements must be met:

- type of PPE must be suitable for the exposure situation;
- PPE must be used during all exposure situations, in all facilities;
- workers must be trained/ PPE program must be in place, to prevent inadequate use;
- PPE must be regularly maintained and cleaned.

4.3.3 Specific applications of EBT

REACH indicates a number of standard information requirements that should be provided in order to register substances. In some cases, the rules set out in column 2 of Annexes VII to X may require certain tests to be undertaken earlier than or in addition to the standard requirements. EBT of testing applies to the repeated dose toxicity studies in Annex VIII-X and the reproduction toxicity study in Annex VIII and may either be proposed by the registrant or may be required by the Agency. There is no general 'adaptation of requirements' leading to general rules for EBT comparable with the general rules for EBW in Annex XI, section 3.

In column 2 of Annex VIII-IX it is indicated that further studies shall be proposed by the registrant or may be required by the Agency in case of particular concern regarding human exposure. No further specification of potential studies that can be proposed is given, however as this remark is given in connection with section 8.6 it is assumed that it only concerns repeated dose toxicity studies. Thus, depending on the exposure scenario, studies can be proposed that are not usually required for the corresponding Annex (e.g. 90-day study in Annex VIII, or 12 month study in Annex IX or X).

Alternatively it can be interpreted that adjustments are made to the standard testing in order to better evaluate the potential toxicity of a substance in conjunction with the exposure scenario. The following may for instance be varied:

- exposure routes
- species experimental animals
- age experimental animals
- special animal models
- concentration of the substance tested
- dosing scheme
- combination with other chemicals

- duration of the study
- specific studies (e.g. aimed to detect neurotoxicity or immunotoxicity)

What exactly encompasses ‘particular concern regarding human exposure’ is not further specified. REACH gives the following two examples:

- use in consumer products leading to exposure levels which are close to the dose levels at which toxicity to humans may be expected (8.6 Annex VIII and IX);
- use in consumer products leading to exposure levels which are close to the dose levels at which toxicity is observed (8.6 Annex X).

Particular concern regarding human exposure is not expected if all available toxicological tests suggest that the substance has a (very) low hazard. So it can be argued that the substance should at least show a relevant hazard in already available tests to consider that there is ‘particular concern’. Next to that aspect, the exposure situation should probably give rise to the expectation that exposure is either (very) high, of long duration and/or high frequency and/or may occur specifically in vulnerable groups. In the specific examples above a dose level and exposure levels should be known.

In addition to the examples given in REACH, several other factors in the exposure scenario may give particular concern regarding human exposure and can therefore justify EBT of testing. These are discussed below.

- Wide-spread use may be reason for EBT of long-term repeated dose toxicity studies and reproduction toxicity studies. Basically, there are two situations in which consumer and worker use can be considered wide-spread.

Firstly, a substance may have many applications and is used in a number of different articles or preparations. Even though the use of these different products when considered separately is not wide-spread or intensive the combined use of these products may be. Wide-spread use can in some cases be a reason for EBT of further studies. For instance, the use of a substance may be chronic when it is present in many different types of products, even though the exposure scenario of the different products on their own is not chronic. In such a case it may be considered to extend the duration of repeated dose toxicity studies beyond those required. Or a more relevant dosing scheme may be needed.

Secondly, a substance on its own, or in a preparation or article may be used frequently and/or for a long duration, thus giving a potential reason for EBT of further testing. In column 2 of Annex VIII and X it is indicated that respectively a sub-chronic toxicity study (90 days) or a long-term repeated toxicity study (≥ 12 months) shall be proposed by the registrant if 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 (Annex VIII).
- Serious or severe toxicity effects of particular concern were observed in the 28-day or 90-day study for which the available evidence is inadequate for toxicological evaluation or risk characterization; or effects shown in substances with a clear relationship in molecular structure with the substance being studied were not detected in the 28-day or 90-day study; or the substance may have a dangerous property that cannot be detected in a 90-day study (Annex X).

On the other hand, frequent, e.g. daily, use, may result in considerable exposure, especially when the exposure duration is long (e.g. as long as people can be expected to spend in their home environment). This may be regarded as ‘particular concern regarding human exposure’ and would thus give reason for EBT of further testing, irrespective of the above given conditions.

- Use is typically aimed at or expected for vulnerable groups:

- Children

As children have the tendency to put things in their mouth, EBT of testing repeated dose toxicity after oral exposure to substances in articles may be considered even though oral exposure is not the most relevant route of exposure for a specific substance. However, before applying EBT also other aspects of the exposure scenario should be taken into account. Firstly, the substance should be released from the article² and oral absorption should occur. Secondly, exposure should be frequently or long-term for the testing of repeated-dose to be relevant. Otherwise it would resemble acute oral toxicity, which is already tested in accordance with the REACH regulation.

Children may be more sensitive to toxicity of certain substances due to differences in absorption, distribution, metabolism and/or elimination as compared to adults. Besides, several systems, among which the nervous, immune, reproductive and skeletal system, undergo substantial postnatal development. For these reasons it may be relevant to trigger studies in juvenile experimental animals in order to study age-specific toxicity and effects on development or growth. However, it may be challenging to design animal experiments that adequately represent the desired human age and stage of development.

- Pregnant women

When the use of a product is specifically aimed at or expected for pregnant women, EBT of additional reproduction toxicity studies may be appropriate. The endpoints of these studies should take both the maternal toxicity and the development toxicity into account.

- Other groups

Some groups of people may be more sensitive for certain substance due to old age, physical fitness, medical conditions or life style. When the use of a product is specifically aimed for such a group, studies should be designed to predict the possible toxicological consequences for this group as specifically as possible. EBT of further testing of the substance in specialized models may be appropriate in these cases. In addition, standard studies may be adjusted or extended and different toxicological endpoints, relevant for the specific vulnerable group, could be included. However, in many cases, it may not be possible to get any specific information on toxic effects in vulnerable groups and triggering of studies is not useful.

Substances used in consumer products in general can lead to exposure to several of the vulnerable groups mentioned above, because these groups are part of the general consumer population. It is clearly not the intention to trigger additional tests for all substances that may be used in consumer products. Therefore, a specific increased exposure (as in children sucking objects) or a specific use for vulnerable groups is required before these vulnerable groups should be seen as a reason for EBT. Similarly, some vulnerable groups also are part of the worker population (pregnant women, atopic individuals), but that cannot be seen as a reason to justify EBT for substances used by workers in general.

- Use of relatively large amounts per day or high concentrations

When a substance is used in relatively large amounts or high concentrations this may be reason for EBT of studies that are not usually required for the tonnage of the substance produced. This is especially relevant when the use is restricted to a specific (small) part of the population, because otherwise the testing requirements under REACH are likely automatically increased as substances that are used in large amounts will be produced in higher tonnage.

Another possibility is when there are uses that occur in aypical work situations with longer than average work shifts and six shifts per week, followed by longer periods off work, such as in off-shore. This may increase the cumulative exposure during certain periods substantially above what is normally assumed (8 hours per day and 5 days per week for workers).

² Oral exposure to *preparations* is considered to be non relevant as it is reasonable to assume that oral exposure will solely be accidental.

Although such situations may lead to higher (cumulative) exposure than usually would be expected, this does not necessarily lead to a justification of EBT. The effect of such specific exposure situations can often be taken into account by a proper combination of assessment factors. However, there may be situations where repeated dose toxicity studies, carcinogenicity or reproduction toxicity studies are not yet required, but where these kinds of exposure aspects may lead to a request for such studies.

- **Multiple exposure routes**

In REACH testing of substances need not necessarily be performed for all exposure routes. For acute toxicity studies it is indicated that the oral route and at least one other exposure route should be studied. For repeated dose toxicity studies and reproduction toxicity studies respectively the most relevant route and the expected route of exposure should be studied. However in certain cases the exposure scenario or physical chemical properties of the substance may show that it is desirable to test more exposure routes. This may be considered a type of EBT.

If the uses and the physicochemical characteristics of the substance and the preparation or article in which it is used lead to possibilities of substantial oral, dermal and inhalation exposure, testing all three routes may scientifically be justified. In workplaces the use of many substances may lead to both inhalation exposure and dermal exposure. When consumer exposure via the oral route can be expected, knowledge on hazards through all routes would be needed. The following aspects may contribute:

- Uses that may lead to aerosol formation of low volatile substances; in these cases both skin contact and inhalation exposure are expected to be relevant.
- Uses of relatively volatile substances in viscous products; this may lead to relevant skin exposure, but also to inhalation of vapours.
- Uses with very frequent or prolonged skin contact with volatiles; skin exposure would be relevant even if the substance evaporates fast from the skin.

In general uptake via the oral route is also possible, via hand-mouth contact after (substantial) skin contamination, and possibly after inhalation of particles that do not pass the upper airways and may be coughed up and swallowed. Therefore, all situations where dermal and inhalation exposure are relevant almost always also include an element of oral exposure. However, as REACH intends to limit the number of animal tests, testing of three exposure routes, specifically with repeated dosing, should only be conducted if there is information that shows that route-to-route extrapolation is not able to reasonably predict the effects or the intensity of effects after exposure via a non-tested route. This may be possible if a different metabolism is to be expected for each route or in case the substance has profound effects at the port of entry (local effects). This should be evaluated based on aspects of absorption, distribution, metabolism and excretion.

4.4 Internal exposure

To recapitulate the general considerations given in section 4.3, exposure based waiving (EBW) and exposure based triggering (EBT) of testing a certain substance is generally based on the external exposure of humans to a substance. In an ITS, the assessment of exposure could be refined (if needed) by taking internal exposure into account for EBW/EBT. In all cases decisions should be based on reliable data.

In general, for internal exposure assessment, the following tests can be performed (including the assessment of one or more of the ADME parameters) as part of the ITS:

- Non-testing methods
 - obtained physical chemical properties
 - using *in silico* approaches
 - (Q)SAR
 - kinetic modelling (e.g. PBTK modelling)
 - using category approach, read-across principles

- Testing methods
 - *In vitro* tests
 - *In vivo* tests

This section will describe how such data could in principle be used for EBW/EBT.

4.4.1 General considerations

The assessment of external exposure could be refined (if needed) by taking internal exposure into account. With specific kinetic experiments and models, EBW/EBT could be applied. This indicates that the internal exposure of a substance could aid the assessment if the external exposure is above the 'no further action level'.

EBW can be applied when it is concluded that after taking internal exposure into account, the predicted substance concentration is below 'no further action level'. If substance specific physicochemical and kinetic properties are relevant for the potential human exposure, additional criteria can be defined.

EBW of testing of a substance can be applied when:

- no oral testing is needed if the absorption of the substance is unlikely;
- no dermal testing is needed if the substance is insoluble or absorption is unlikely;
- no inhalation testing is needed if the substance is not a gas, vapour or dust (below a defined particle size) or if the substance is a liquid with high enough vapour pressure. Care must be taken to clarify what vapour is so that 'semi-volatile' compounds are not excluded;
- no inhalation testing is needed if absorption of the substance is unlikely;
- solid produced as non-abrasive large granules or flakes.

Based on the above situations, specific criteria need to be described that can be used as guidance for EBW of testing a substance. Such criteria should include the reliability of the data, the effect of vehicles and matrices and of modes of administration.

EBT can be applied when there is considerable concern regarding human exposure of the substance. For specific settings, it can be expected that substance specific physicochemical and kinetic properties are relevant for EBT of testing a substance.

EBT of testing a substance can be applied if:

- distribution experiments indicate bioaccumulation in specific parts of the body;
- the metabolites of the substance are of more concern than the parent compound (bioactivation);
- the substance is used in products (vehicles) that enhance absorption (dermal, inhalatory, oral).

Based on the above situations, specific criteria need to be described that can be used as guidance for EBT of testing a substance.

Based mainly on the above-mentioned situations, the following should be read as a first suggestion for criteria and (semi)quantification thereof. It is open for further discussion within OSIRIS WP 3.3 as well as WP 3.2 (External exposure). It is noted that a combination of two or more criteria that are fulfilled for either EBW or EBT should be regarded as a stronger criterion for EBW or EBT, respectively, than only a single criterion.

It should be kept in mind that the uncertainty for predicting the internal exposure of unknown chemicals for REACH (risk assessment purposes) needs specific requirements. For example, a difference between 50% and 100% (oral, dermal, inhalatory) absorption of a compound represents a factor 2 in outcome. A difference between 1% and 10 % absorption would be more critical, since this represents a factor of 10 in the risk assessment. For this reason, the test strategies designed by the pharmaceutical industries should be validated for risk assessment purposes and EBW.

We are aware that the question where external exposure stops and where does internal exposure start, or even on the question whether there is an intermediate interface in between is difficult to answer. A discussion on this topic is needed E.g. should the limitation of alveoli to particles $>5\text{ }\mu\text{m}$ be a criterion for External EBW or for Internal EBW?

4.4.2 Non-testing methods

4.4.2.1 Obtained physical chemical properties

The toxicokinetic parameters that need to be predicted are named ADME (Absorption, Distribution, Metabolism and Excretion) parameters. These kinetic processes and their role in EBW/EBT for testing a substance are described below in more detail.

Absorption

In order for a substance to be absorbed, it must cross biological membranes. According to and based on the TGD (EC, 2003; EC, 2007b), absorption of compounds by various routes (oral, dermal and inhalatory) are likely to be impaired when some of the criteria are valid:

- Oral exposure
 - Based on mainly physico-chemical substance specific properties a prediction can be made whether the oral absorption of a substance is likely to be impaired. This can be an indication for EBW or EBT of testing oral exposure of a compound. These indications are:
 - when $\log K_{ow}$ (where K_{ow} is the *n*-octanol/water partition coefficient) is below -2 or above +7, oral absorption may be impaired
 - when MW > 1000, oral absorption of the substance may be impaired
 - high water solubility (very hydrophilic substances) may limit oral absorption by passive diffusion
 - oral absorption of 'very large' particles (>100 μ m) in the GIT (gastrointestinal tract) is reduced because of the time for the particle to dissolve (for poorly dissolvable substances)
 - rapid hydrolysis of the parent compound in the GI-tract may impair the bioavailability of the parent compound and the toxicokinetic predictions based on the parent compound may not be relevant without taking this into account.
 - Exposure via inhalation
 - Physico-chemical properties that in general do influence internal and/or external exposure via inhalation are melting point, boiling point and vapor pressure at ambient temperature. For inhalation, above stated requirements concerning molecular weight and K_{ow} are also valid. These physico-chemical properties can be an indication for EBW of testing exposure via inhalation. These indications are:
 - Highly volatile compounds (compounds with a vapour pressure above 25 kPa, or a boiling point below 50 °C) will be prone to enter the body by the inhalation route. Conversely, a low vapour pressure, (> 0.5 kPa or a boiling point above 150 °C) will consequently result in a low vaporisation of the substance. This limits exposure via inhalation.
 - Emission of vapour is considered to be negligible in case of solid substances with a vapour pressure smaller than 1 kPa (at process temperature) and liquids with a vapour pressure smaller than 0.1 kPa (at process temperature) (Bunke et al., 2006).
 - The disposition of inhaled particles in the airways depends on the particles size. As a rough guide, particles with aerodynamic diameter below 100 μ m have the potential to be inhaled. Of the inhaled particles, diameters below 5 μ m are most likely to settle in the tracheobronchial or pulmonary regions. Above 5 μ m, the particles have the greatest probability of settling in the nasopharyngeal regions. But even there, subsequent dissolution of chemicals or molecules from the particle may result in absorption in the nasopharyngeal regions.
 - Rapid hydrolysis of the parent compound in the lung may impair the bioavailability of the parent compound and the toxicokinetic predictions based on the parent compound may not be relevant without taking this into account.
 - After inhalation of particles, coughing up and swallowing may result in oral exposure and absorption.
 - Dermal exposure
 - Substances that can potentially be taken up across the skin include gases and vapours, liquids and particulates. For EBW or EBT of testing dermal exposure of substances, the following preliminary indications can be identified.

- Dry particulates are not readily absorbed by the skin. These dry particulates will have to dissolve into the surface moisture of the skin. Absorption of volatile liquids across the skin may be limited by the rate at which the liquid evaporates off the skin surface. A criterion could be:
 - Full evaporation of high levels of contamination can be expected in a matter of minutes (say < 10 minutes), and
 - Duration of exposure is not more than 10 minutes consecutively and frequency not more than four times per day.
- MW < 100 favours dermal uptake; MW > 500 may impair dermal absorption.
- When $\log K_{ow} < -1$, the substance is not likely to be absorbed. When $\log K_{ow} > 6$, the rate of transfer between the stratum corneum and the epidermis will be slow and will limit absorption across the skin.
- If the surface tension of an aqueous solution is less than 10 mN/m, the substance is a surfactant and this will enhance potential dermal uptake. Also dermal absorption of other compounds in contact with the surfactant may be enhanced

Distribution

The physicochemical characteristic of the parent substance can, sometimes, give an indication on the distribution. In general, substances and their metabolites that readily diffuse across membranes will distribute through the body and may be able to cross specific barriers (blood-brain, blood-testes, and placenta)

The physicochemical characteristics that give information on the extent of distribution are:

1. The smaller the molecule, the wider the distribution
2. If the molecule is lipophilic ($\log K_{ow} > 0$), the substance is likely to distribute into cells

With the distribution, also specific (bio) accumulation should be taken into account. This represents the potential for a substance to accumulate or to be retained within the body. Highly lipophilic substances ($\log K_{ow} > 4$) tend to have longer half-lives. These substances can accumulate in the body. Such criteria will be addressed in the OSIRIS project.

Metabolism

Differences in the way substances are metabolised by different species and within different tissues, is the main reason for species- and route- specific toxicity. Although it is very difficult to predict, purely on the basis of physico-chemical data, what metabolic changes a substance may undergo, specific structures in the molecule are known to be more or less prone to specific physico-chemical or biochemical (enzymes) conversion.

Knowledge on the (possible) active metabolites of a parent compound and whether this/these metabolite(s) are identical to metabolites of data-rich substances may be used as an argument in EBW or EBT.

Excretion

There is a limited number of conclusions that can be drawn purely from physico-chemical data about the excretion of a substance from the body. The major routes for excretion of substances from the systemic circulation are urine and/or faeces. The minor routes, exhaled air, breast milk, sweat and saliva are also discussed.

Urine

- Highly water soluble substances favour urine excretion
- Low MW (MW < 300 in rats) favours urinary excretion.

Bile (faeces)

- In rats, organic cations having MW < 300 are unlikely to be excreted for more than 5-10% with bile. Organic anions and quaternary ammonium ions are even less susceptible for bile secretion.
- Molecules that are amphipathic (containing both polar and non-polar regions), hydrophobic/strong polar and have a high molecular weight are susceptible for biliary secretion.

- Substances in bile may, potentially, undergo enterohepatic circulation. Especially conjugated substances can undergo this route.

Exhaled air

- Vapours, gasses and volatile liquids/metabolites may be excreted via the lungs through exhaled air

Breast milk

- All substances present in plasma are also found in breast milk. Lipid compounds may have a higher concentration in breast milk as of its relatively high fat content.

Saliva/sweat

- Non-ionised and lipid soluble compounds may be excreted by saliva and sweat.

Skin Scale

- Lipophilic chemicals may be excreted by shedding of the epidermis.

4.4.2.2 Using *in silico* approaches

(Q)SAR

Up till now, no data is available that indicate internal exposure founded EBW based on (Q)SAR experiments.

Kinetic modelling (e.g. PBTK modelling)

Sophisticated kinetic models (including PBTK models) could, in principle, predict the concentration – time profile of a compound in the body. These models are highly data demanding and as such, are not frequently used up till now in chemical risk assessment. In a recent article, a list of various PBTK models that are used by risk assessment/regulatory agencies was published (Loizou et al., 2008). The compounds in these models have already been assessed. For new substances, it would be a challenge to collect the amount of data needed for PBTK modelling. New substances often will be outside the domain of the models. Up till now, no data is available that indicate internal exposure founded EBW/EBT based on kinetic modelling.

4.4.2.3 Using Category approaches, read-across

A chemical category is a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity (US EPA, 1999). Generally, not all chemicals in a defined category need a complete set of test data in order to address all health and environmental endpoints. Toxicology and kinetic data available for some chemicals in the category for a given endpoint can be used to estimate or otherwise infer (e.g. through interpolation or extrapolation) that analogous values for related category members that lack such data (also called ‘read-across’) (US EPA, 2005). This indicates that EBT/EBW could be applied on the basis of similarities with known substances (criteria needed).

4.4.3 Testing methods

4.4.3.1 *In vitro* tests

To date, a limited amount of *in vitro* tests could be used for EBW. These studies only deal with dermal exposure. More research is needed to explore the role of other *in vitro* tests in EBW.

Absorption

Dermal: To determine the passage of a compound through the skin, alternative *in vitro* methods exist. The OECD 428 Skin Absorption: *in vitro* model can be used to examine if a compound will be absorbed through skin or not. A very low dermal absorption could be a reason for EBW if dermal exposure is the main exposure route (criteria needed).

Oral: Although *in vitro* oral absorption has not been described with validated OECD guidelines, these *in vitro* studies will give an indication of the internal exposure after oral exposure to a compound. To determine oral absorption of a compound, no OECD guidelines for testing exist. However, there are several common high throughput membrane studies (e.g. Caco-2 cell line or artificial PAMPA membranes) that will give a basal idea if passive transport over the GIT will occur. For industrial chemicals, these *in vitro* membrane studies could indicate whether a compound will be able to pass a

membrane. A low passage of the *in vitro* membranes could be a reason for EBW if oral exposure is the main exposure route (Versantvoort et al., 2000).

Distribution

Distribution refers to the reversible transfer of a substance from one location to another within the body. As such, also bioaccumulation should be taken into account. The ability and magnitude of a compound to bioaccumulation in (a specific organ in) the body could result in classification and labelling of that compound as PBT. This could result in EBT for additional tests. However, up till now, no data is available that indicate internal exposure founded EBT based on *in vitro* distribution experiments

Metabolism

Metabolism (biotransformation) represents the biochemical conversion of a parent compound to its metabolites. The majority of the metabolites formed by biotransformation are inactive, but sometimes, bioactivation can occur. This bioactivation of a compound by metabolism could be a reason for EBT. *In vitro* metabolism studies could be used to test the metabolism of the parent compound and its (bioactive) metabolites. However, up till now, no data is available that indicate internal exposure founded EBT based on *in vitro* metabolism experiments.

Excretion

Up till now, no data is available that indicate internal exposure founded EBW based on *in vitro* excretion experiments.

4.4.3.2 (Optimized) *in vivo* tests

The goal of an Intelligent Testing Strategy is to retrieve as much data as possible from experiments. Therefore, it should be encouraged to take additional kinetic endpoints in standard OECD *in vivo* toxicity test. Furthermore, satellite groups can be added in the OECD protocol. It is possible that studies in a higher annex (tonnage level) could be waved based on the additional kinetic (and other) information gathered with these OECD toxicity tests/satellite groups.

In addition, a kinetic *in vivo* study with only a limited number of animals could already indicate the bioavailability of a compound after oral/dermal/inhalatory exposure. These non-OECD *in vivo* tests could be a reason for EBW of further OECD toxicity tests if the previous experiments only indicate very low bioavailability (criteria needed).

5 Needs for exposure assessment methodology

5.1 Introduction

This chapter will discuss the risk-based approach towards EBW/EBT. Following a discussion of uncertainty and variability in this risk-based approach, criteria will be discussed for exposure modelling. Reference is made to the ‘Technical guidance document for preparing the chemical safety assessment, Part E: Risk Characterization’ (EC, 2007e).

5.2 Uncertainty and variability

In REACH (EC, 2007a, Annex I), the level of risk is characterised by means of the quotient of exposure and effect parameters. This quotient usually is a point estimate. To avoid an underestimation of potential risk, a worst-case approach can be followed by choosing a worst-case exposure scenario with the worst possible emission factors, model parameters and environmental conditions. Such an accumulation of worst cases may, however, eventually lead to unrealistically high risk levels which are extremely unlikely to occur. Therefore, usually a ‘reasonable worst-case’ risk assessment is performed (EC, 2007f). The chosen standard exposure scenario represents an unfavourable, but not unrealistic, situation. However, for the model parameters, mean, median or typical values will be used in most cases. The effect parameters DNEL and PNEC can be considered conservative point estimates derived via application of assessment factors. Thresholds of Toxicological Concern are worst case values derived using probabilistic techniques (5th percentile of cumulative distributions of no-effect levels, see section 3.3).

As described in Section 4.2, for EBW and EBT exposure values also have to be compared to a no- or minimal effect level which is either specific for the substance or a general threshold like TTC. For EBW it is required that the qualitatively or quantitatively estimated exposure is sufficiently below the no- or minimal effect level. Both the exposure and the no- or minimal effect measure are uncertain because of uncertainties and variability in scenarios, models, and parameters, leading theoretically to a distribution of risk characterization ratios like PEC/PNEC (Figure 5), estimated Intake/DNEL, PEC/ETNC, Estimated Intake/TTC. Therefore the real question is what the probability is that the estimated risk characterization ratio is still exceeding the trigger value of 1 and if so, if that still warrants the conclusion that EBW is acceptable. If the distribution is such that only the far right end of it is exceeding the trigger value (Figure 5, steep curve A), EBW may be acceptable. Alternatively, a tier 1 realistic worst case assessment can be performed the result of which can be considered to be equivalent a ‘far right end’ estimate. If a significant part of the distribution exceeds the trigger value (Figure 5, shallow curve B), EBW should be declined. Conversely, distributions far above one would trigger testing.

It is noted that the concept is still applicable when only qualitative indications of exposure are available. In this approach, uncertainties are treated qualitatively and could lead to a rough indication of the magnitude of risk, i.e. the qualitative probability that the risk characterization ratio would be far below 1 (enabling EBW), around 1 (no EBW) or far above 1 (refinement or EBT).

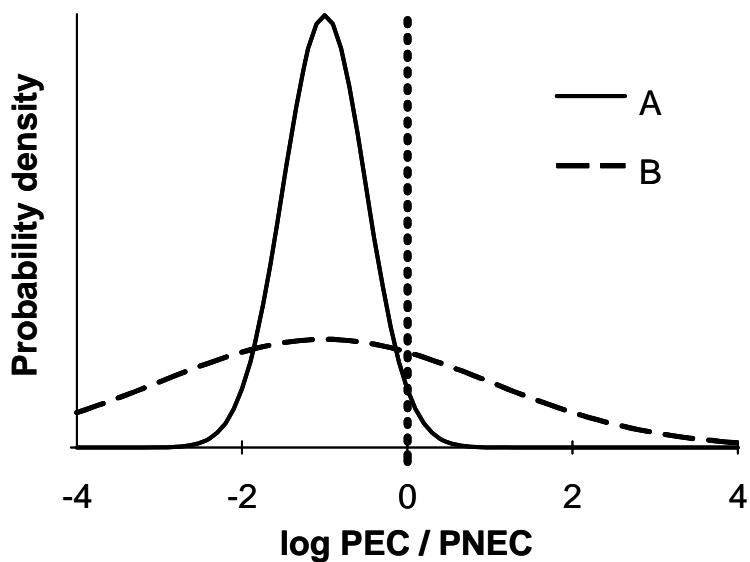


Figure 5: Uncertainty in the risk characterization (Jager et al., 2001)

5.3 Criteria for exposure estimation

5.3.1 Environmental exposure

5.3.1.1 Introduction

Two types of situations can be distinguished with regard to EBW (chapter 3):

1. situations which do not require further exposure assessment because exposure is very likely too low to require hazard testing.
2. situations that require exposure models or other methods to indicate that use results in exposure levels below the level of 'no further action' (i.e. situation 1 does not apply).

In chemical safety assessments environmental exposure levels at defined Exposure Scenarios can be assessed by means of either measured data or model estimates. For many chemicals information on actual exposure doses or concentrations is limited or even absent and concentrations generally vary significantly in time and space.

Measurements encompasses both actual measured concentrations and measured values that can be used to refine the exposure calculation, e.g. measured release fractions or emission rates, measured removals in sewage treatment facilities. Measurement data can be used to indicate that exposures are below levels at which there is no need to gather further hazard data, because this will not influence the conclusions on the risk management measures needed for safe use. Alternatively, measured data can indicate that exposure levels in certain situations can be very high and thus contribute to the justification of EBT.

To enable the use of measurement data (together with available hazard information) for EBW or EBT, the data need to be representative for the Exposure Scenario concerned and of sufficient quality. It should be clear where the data fit in the distribution of exposure levels, for instance, whether they are worst case, maximum, average or x^{th} percentile (see Reference TGD, chapter R16.3; EC, 2007g).

Doses and environmental concentrations of a chemical are predicted in a two-step procedure under REACH. Firstly, releases to environmental compartments or the indoor environment are predicted based on the Exposure Scenario (including volume produced, imported or used, the conditions of use, the RMMs applied and physico-chemical properties of the chemical concerned). Next, environmental concentrations and human daily intake doses are calculated using mathematical models, which take into account the transport and fate of the substance.

5.3.1.2 Environmental release estimation

Introduction

The production and use of chemicals and the resulting environmental exposure can be described by use and release patterns. A substance can be emitted during its various life cycle stages starting at production, through formulation, use and various waste treatment options at the end. The emission rate depends on the substance properties like volatility and solubility, the technical function of the substance and the industrial area (economic sector) where the substance is applied. The industrial area gives an indication of the kind of processes applied and the type of equipment used. Depending on the combinations of these elements releases are more or less likely to occur. Some combinations are even not likely or may not be relevant with respect to the release to the environmental compartments air, water and soil. Presets of use and release descriptors which may provide a trigger for prioritization in chemical safety assessment will be identified and thus support the development of intelligent testing strategies in Chemical Safety Assessment. The analysis will focus on environmental compartments air, water and soil.

Direct release to soil from production, use or the waste stage, refers to industrial soil, which is not an endpoint in chemical safety assessment. Only agricultural soil and natural soil are to be considered but there is in general no direct release to these types of soil with the exception of agrochemicals and biocides, which are not part of the REACH regulation. Both agricultural soil and natural soil are only indirectly exposed either via the atmosphere through wet and dry deposition or through the application of sewage sludge on agricultural soil only. Therefore industrial soil will not be considered explicitly.

The possible combinations of the elements of the use and release patterns of a substance, which might aid the chemical safety assessment, will have to be identified from the release assessment procedures in the current guidance for risk assessment. The approach will be qualitatively at first and should be based on recent guidance (REACH). For a start the analysis is based on the previous guidance, provided by the TGD (EC, 2003) for new and existing substance, on release estimation. These emission estimation methods are not explicitly excluded from the new guidance for REACH and provide more detailed considerations on release estimation like for instance substance properties and technical functions of chemicals.

Criteria for release aim at the prioritisation or the focus of the risk assessment. From the perspective of waiving, the emphasis will be on situations or combinations of release descriptors which will lead to little or no emissions to air, water or soil to be expected.

Next to the information available from the guidance on chemical safety assessment and the risk assessment of new and existing substances, past experiences from risk assessments of new and existing chemicals are also considered. Specific situations from these experiences which might aid the chemical safety assessment will also be described.

Finally there will be special attention to the use of risk management measures, which have a prominent place in the procedure of chemical safety assessment.

A. Criteria based on release descriptors

As stated in the introduction, criteria for release can be based on the following descriptors: substance properties, process conditions and type of use and the application area (industrial sector).

Several criteria describing (use and) release patterns will be considered in this section. The focus will be on substance properties and combinations of the application area and the technical or chemical function of a substance at first instance. Possible criteria will be described per life cycle stage and per compartment.

The most relevant substance properties in release estimation are the vapour pressure and the water solubility of the substance. In a few cases other substance properties like the octanol-water partition coefficient and the air-water partition coefficient are relevant.

In addition to the substance properties, process conditions or the type of process and type of equipment are discriminating factors. These factors are being described by main categories according to the old and new guidance for release estimation (EC, 2003; EC, 2007g). There are several main categories to be distinguished: inclusion into or onto a matrix, industrial equipment (non dispersive), wide dispersive use (public at large), of which some have several sub-categories.

Production of substances

Air

For the life cycle stage of production a distinction has to be made between intermediates and other substances not used as intermediates (non-intermediates). Furthermore the main process categories are not the same for the production of intermediates and other substances. The emission to air can be considered negligible for substances other than intermediates, with a vapour pressure lower than 10 Pa and produced in a continuous production process (a, Table 2) or with a vapour pressure lower than 1 Pa and produced with dedicated equipment (b).

The release to air can also be considered negligible for, the production of non-isolated intermediates (a) with a vapour pressure < 100 Pa, the production of isolated intermediates stored on-site (b) with a vapour pressure < 10 Pa and transported isolated intermediates (c) with a vapour pressure < 1 Pa. The release of substances produced in multi-purpose equipment (d) cannot be considered negligible, without considering any additional specific risk reduction measures.

Table 2: Criteria based on vapour pressure (Pa) for negligible release of substances to air production

| Type of substance | Main process category | | | |
|--------------------------|------------------------------|----------|----------|----------|
| | a | b | c | d |
| non-intermediates | < 10 | < 1 | - | - |
| intermediates | < 100 | < 10 | < 1 | n.r. |

n.r. = not relevant

- = no criteria to be derived

a, b, c, d = main process categories a, b, c, d have been described in the text.

Industrial soil

For soil (industrial) the emission is expected to be negligible at the production of non-isolated intermediates only.

Waste water

For waste water there is always a considerable emission (0.2-6 %) to be expected, not taking specific process conditions or measures into account. Therefore for water there are no specific criteria to be derived other than specific process conditions or risk management measures.

Formulation of substances into articles or products

Both for air and waste water there are always considerable releases to be expected, the extent is depending on the type of equipment and operation routines. Releases increase from dedicated equipment with very little cleaning operations to dedicated equipment with frequent cleaning operations to multi-purpose equipment. For substances used in the photographic industry for the control of crystal growth the emission to air is expected to be negligible at the formulation stage in the manufacture of solid materials (photographic films). This is the only situation for the formulation stage where based on the technical function of the substance release can be considered negligible according to the general release tables.

Processing within the industry and use by the public at large and public domain

For industrial use (processing) and use by the public at large and within the public domain (hospitals, hotels, offices etc.) it is very difficult to derive general criteria only based on the vapour pressure and the water solubility. As stated before release does not only depend on substance properties but also on the technical function of the chemical and the application area (industrial sector).

The technical function of substance might be suitable as this is one of the key descriptors in deriving release factors. But before considering specific technical functions of chemicals, it should be noted that a substance can be categorised into processing aid and a substance which becomes part of a product or a closed system. Examples of the latter are plasticizers used in plastic articles and substances used in capacitors as a dielectric medium. In the former case a substance is physically bound to a substrate or material commonly referred to as inclusion into or onto a matrix and release to the environment will be limited. Processing aids are generally emitted to air during processing and/or released into waste water and become waste materials.

But, even for substances which are intended to be included into or onto a matrix during processing, it is not straight forward to give clear criteria. For instance from the most general release estimates for processing into or onto a matrix it can be derived that the atmospheric release for substances with a vapour pressure lower than 10 Pa can be considered negligible. This still holds for the paper and board industry and paints, lacquers and varnishes industry but does not hold for instance for the textile and the leather processing industry and the polymers industry.

It is therefore suggested to draw up criteria for industrial sectors separately with regard to the life cycle stage processing. Furthermore the technical function of a substance seems more appropriate as a starting point than substance properties.

A selection was made of combinations of the technical function of a chemical and the industrial sector where the substance is used (Table 4). The (industrial) sector where a substance is applied gives a rough indication of the type of equipment and technology commonly used in that sector and to which extend certain provisions have been implemented

From the analysis some general conclusions can be drawn, for instance propellants used in aerosol cans are not expected to be released to water or soil at application. Colouring agents for example applied by the public at large (textile dyeing) or in the printing industry are not expected to be emitted to the atmosphere. Substances like fillers, surface active ingredients and colouring agents in paints, lacquers and varnishes are not expected to be finally released to the atmosphere due to the use of these products and therefore the focus should be on the aquatic compartment. As a final example the release into waste water of solvents used at processing of polymers like calendaring, extrusion, injection moulding and press moulding is expected to be negligible.

****B. Criteria based on process descriptions****

Experiences from the risk assessment of chemicals provide useful information, which may be suitable for deriving criteria for exposure based waiving. Some general leads from these experiences have been formulated for each environmental compartment. These leads serve more or less as examples and there may be more general or specific descriptions of how to deal with specific situations in chemical risk assessment or chemical safety assessment which can be of help in exposure based waving.

Table 3: Selection of the relevant compartments (A=air; W=water and S=soil) for the use of certain types of chemicals within a specific sector

| Application area | Technical function* | A | W | S |
|--|--|---|---|---|
| Agriculture | Cleaning and washing agents, pharmaceuticals, food and feedstuff additives | 0 | x | x |
| Public at large | Bleaching agents, cleaning and washing agents, colouring agents, complexing agents, pharmaceuticals, softeners, surface active ingredients, photochemicals | 0 | x | x |
| Agriculture, public at large, paints, lacquers and varnishes | Aerosol propellants | x | 0 | 0 |
| Polymer processing in the polymers industry | Solvents | x | 0 | x |
| Paints, lacquers and varnishes industry | Fillers, surface active ingredients, colouring agents | 0 | x | x |

* The technical function is provided for those compartments with negligible release.

0 = no or negligible release to be expected

x = possible release

Air

Under specific process conditions release to air will be minimal. The specific conditions or equipment generally referred to is use or production in closed equipment. Systems or equipment is easily labelled as 'closed', meaning that there is no direct contact with the surrounding atmosphere. This is something different than the meaning of closed systems related to the release of substances from the equipment to the surrounding atmosphere. Only very special equipment with gastight seals and other special provisions to prevent gas leaks may be considered as closed systems. This type of equipment will generally only be found in industrial areas handling very toxic compounds for instance cyanides with the possibility of workers getting in contact with these compounds.

Releases to air are expected to be negligible in those situations where gastight equipment is used and special provisions are installed to prevent the release of captured process gasses into the environment. To prevent hazardous substances to be released within the process facility usually worker exposure measures will be in place for instance local exhaust ventilation. After capture the waste gas streams usually will be vented to the environment. To prevent unwanted environmental exposure, risk reduction measures like end-of pipe waste gas treatment equipment may be installed, see section C.

Soil

For the local risk assessment direct release to soil is not taken into account. A substance might end up in the local soil indirectly via atmospheric deposition (dry and wet) and through the use of sewage sludge as a fertilizer. Two routes contribute to atmospheric deposition, firstly through atmospheric release from the local facility and secondly through volatilization from the sewage treatment plant. The contribution of sewage sludge to release into the environment can be excluded when the sludge is treated as chemical waste and burned in incinerators. This is usually the case for on-site biological waste water treatment facilities. For public owned sewage treatment plants this depends on the national regulations. By default the route of sewage sludge public sewage treatment plants is included in the risk assessment.

Water

Release to surface water can be limited or prevented due to on-site measures. This can be established when appropriate measures are in place to prevent releases to waste water through either process integrated measures or end-of pipe techniques. As a process integrated measure the exclusion of water from the process can be considered. Release to waste water is not expected in case there is no water used in the process (dry process) and no water is used for cleaning operations. Cleaning operations can be sub-divided into cleaning process equipment or cleaning the production facility (floor, walls etc.). In

the paint, lacquers and varnish industry and the pharmaceutical industry, batch processes are quite common and equipment has to be cleaned frequently before running a new batch. Cleaning can be done by using organic solvents instead, without the use of water. The solvent can be recycled or re-used in the next batch process. Another, end-off pipe measure leading to no release to waste water is the collection of contaminated process water, which is to be treated as chemical waste. Section C provides options for treating collected waste water, for instance waste water incineration with very high efficiencies.

Thus, release to waste water is expected to be minimal when there is no water used in the process or in cleaning operations for the equipment and the working area or when waste water is collected and treated as chemical waste for instance through incineration. Under these specific conditions a risk assessment for the water compartment can be excluded.

C. Risk management measures, end-off pipe techniques

Release to the environment can be reduced through the implementation of specific measures either process integrated or end-off pipe techniques. End-off pipe techniques are used to treat process waste streams to air, water or soil in order to reduce or eliminate the environmental load.

An important factor in preventing release to the environment is the capture efficiency. The capture efficiency relates to the specific fraction of the process releases which is being treated by the end-of pipe equipment. The capture efficiency should also be near to 100% for a RMM to be optimal efficient. But this cannot always be achieved. For instance gaseous process release from pipe sealings, flanges, ducts, etc. are difficult to be captured.

Air

For waste gas streams vented to the atmosphere the most common techniques to prevent or reduce release to the environment are scrubbers, filters, cyclones and incinerators. Incinerators and scrubbers can have very high efficiencies in the range of >99% but this very strongly depends on the type of substance (organic, inorganic, acid, base etc.) and the physical state of the substance whilst being emitted (gas, vapour, aerosol, dust) and the load in the waste stream.

Release to air will be minimal for those facilities using gas tight equipment, see section 3, where process emissions are completely being captured and the reduction efficiency of the measures is very high, more than 99.9 % or higher.

Generally the suitable treatment option depends very much on the physical state and form of the contaminant being either solid (dust, granules), liquid (mist, aerosols, droplets) or gaseous. For dust and aerosols, filters and cyclones with a maximum efficiency 90-99% can be applied. For dust, aerosols and gaseous waste streams, wet and dry scrubbers can be used depending on type of substance and physical states efficiencies usually vary from 80->99%. Gaseous emission can be treated in incinerators (thermal, catalytic) with treatment efficiencies in the range of 90->99.9%.

Water

Potential end-off pipe measures to reduce or prevent release to waste water are numerous. Only very few though have sufficiently high efficiencies and most of the time for specific cases and related compounds, that release can be assumed to be negligible before hand. Common end-off pipe technologies used to treat waste water can be divided into physical, chemical and biological methods. Physical methods can be sub-divided into mechanical and physical methods or a combination of these two methods. Physical methods like strippers, extraction units and adsorbers usually have high efficiencies of about 90% or higher. Filtration methods using membranes like nanofiltration, reverse osmosis and micro filtration can have high efficiencies of about 99%. But the efficiencies strongly depend on the process conditions, the physical form of the substance and substance properties. Of the

chemical processes only methods applying oxidation have high efficiencies in the range of 80-> 99.9% for instance chemical oxidation, wet air oxidation (super critical and high pressure) and waste water incineration. For many other chemical methods like precipitation coagulation and electrolysis it is not possible to give efficiencies before hand. The maximum efficiencies very much depend on the local situation, process conditions and substance properties. For biological methods (activated sludge, anaerobic and aerobic degradation) for instance the treatment of sewage in sewage treatment plants (STP) the removal efficiency depends largely on the biodegradability and the physical properties of the specific compound. Calculations with the SimpleTreat 3.0 model indicated that for non-biodegradable compounds the removal from waste water is about 95% for very volatile and insoluble compounds with a log Henry of 4 or higher. For compounds with a log Henry of 3 or higher the removal efficiency is at least 90%. The removal is largely caused by the stripping effect in the aerator tank of the STP. For substances with a very high octanol-water partition coefficient, log K_{ow} of 6 or higher, the main removal route is through sludge, maximum value about 85% for non-volatile and non-biodegradable compounds. Only for ready biodegradable compounds with a half live of about 40 minutes, the degradation is about 90% depending of course on its ability to bind to suspended matter and the Henry constant. The maximum removal efficiencies for STP is in the range of 97-98 percent based on a combination of stripping to air, binding to suspended matter and or (bio)degradation.

Conclusions

For the life cycle stage production some distinct criteria for exposure based waiving for the air compartment can be derived for different classes of production processes. The criteria are based on the vapour pressure of the substance. For the other life cycle stages (formulation and use) and compartments (water and soil), there is no straightforward way to derive criteria based on substance properties. In these cases the technical function of a substance can be used in combination with the industrial sector where the substance is used. In some cases the criteria are independent of the industrial sector. Next to the substance properties and technical functions of a chemical general process descriptions have been described and discussed, which can be use in exposure based waiving. The descriptions are very general and should always be checked whether common practice satisfies the criteria for specific types of industry or production processes. Finally, various risk management measures have been discussed. It is clear that it is difficult to derive general criteria from risk management measures. The efficiency of the measure might differ from case to case. There are only few techniques available with very high efficiencies. These techniques can be used as a kind of criterion for exposure based waiving.

5.3.1.3 Modelling

From section 3.2 it can be concluded that for EBW and EBT insight is needed into the uncertainty and variability of the models used, i.e.:

1. insight into the validation status of the models
2. insight into the variability of parameter values
3. insight into uncertainty of parameter values

The basis of the environmental exposure assessment in the TGD is EUSES. A strict validation of systems like EUSES is not possible. The result of EUSES is a risk estimate³: a PEC/PNEC quotient (quotient of the Predicted Environmental Concentration and the Predicted No-Effect Concentration for an endpoint) or an Estimated intake /DNEL quotient (quotient of a predicted intake level and the Derived-No-Effect level). These risk estimates are abstractions and cannot be determined in the real world. Nevertheless, an evaluation in a less strict manner should be performed to clarify the degree of confidence in the final results. Parts of the system (modules or models) can be validated numerically. Exposure concentrations can be measured but one has to realise that the measured data usually are not representative for the model situation described by EUSES for two reasons:

³ Strictly speaking, these quotients are not risk estimates as they do not quantify the incidence and severity of toxic effects. They are merely surrogate indicators for the unknown risk.

1. In the absence of specific data, several chemical-specific parameters are set to worst-case values (e.g. release rates, degradation rates) and the assessment is performed for a worst-case exposure scenario, the so-called 'standard environment'. Measured field data will invariably be non-representative for this situation. The concept of a standard scenario clearly plays a crucial role in the assessment and its applicability and appropriateness should be considered in a model validation.
2. Most variations in time and space are averaged out in EUSES.

The use of a standard scenario does not mean that EUSES is 'not valid'. In fact, the purpose of EUSES is not to predict actual effects or concentrations occurring in the environment. In fact, the system will provide the user with a conservative estimate for a non-existing standard environment, based on limited data requirements. There are much better models or systems for the purpose of exposure prediction but they operate at much higher data needs and only for specific locations. The main purpose of EUSES is to distinguish potentially risky chemicals from chemicals that are likely to be 'safe', based on a limited amount of data, and to indicate where further data are needed to reach confident decisions. Naturally, this purpose will be served by appropriate and numerically valid sub-models but this should not be seen as a prerequisite for validity of the system as a whole

Validation studies of submodules of EUSES 1.0 have been carried out and summarized by Jager ed. (1998) (see Table 4). It was noted that validation activities for individual models are seldom directly applicable to EUSES, since this is a generic instrument, using a fixed, standard scenario. The regional model Simplebox has also been subject to validation studies (Berding, 2000; Struijs and Peijnenburg, 2002). Berding compared the model results with measurement for a wide range of chemicals and concluded that the model complies with its purpose to calculated regional background concentrations. Struijs and Peijnenburg compared predicted and measured air/water concentrations for two phthalate esters and found that these concentrations did not differ more than a factor of 10 if measured partitioning coefficients were used. In both studies, the overall result was greatly affected by uncertainty in emission data.

A detailed 3-year validation study of EUSES 1.0 has been carried out for single submodels on the one hand and the entire system on the other (Schwartz et al., 1998; Schwartz, 2000). Regarding the software, EUSES was found to basically fulfil the postulated quality criteria. However, high complexity, low modularity and incomplete documentation were concluded to result in lack of transparency. The performance of the model was characterised as a good compromise between complexity and practicability. It was noted that, in a strict sense, the method is only applicable for persistent, non-dissociating substances of intermediate lipophilicity.

Table 4: Summary of the validation status of the EUSES sub-modules (Jager ed., 1998)

| Module | Conservatism | Indication of possible deviation from measured values |
|--|---|---|
| Release estimation | Worst case | 1 - 1000 |
| Environmental distribution <i>partition coefficients</i> <i>biodegradation rates</i> <i>sewage treatment</i> <i>local distribution</i> <i>regional distribution</i> | median estimate generally worst case median case largely unknown, scenario worst case optimistic case | up to factor of 15 for high K_{ow} 0.1 - 100 within factor of 10 unknown 0.001-10 |
| Exposure <i>BCFs</i> <i>drinking water</i> <i>total dose</i> | usually median case worst case worst case | within a factor of 100 unknown unknown |
| Consumer exposure | worst-case scenario | unknown |
| Workplace exposure | generally worst-case | 0.1-1000 |
| Effects assessment <i>environment</i> <i>human</i> | generally worst case unknown | 0.5-1000 unknown |

5.3.2 Human exposure

In chemical safety assessments consumer and worker exposure levels at defined exposure scenarios can be assessed by means of either measurement data and/or model estimates. The possible usefulness of these methods in the scope of Exposure Informed Testing is discussed briefly below.

Measured data

Measured data can be used to indicate that exposures are below 'no further action levels'. Alternatively, measured data can indicate that exposure levels in certain situations can be very high and thus might contribute to the justification of EBT. To enable the use of measured data (together with available hazard information) for EBW or EBT, the data need to be representative and of sufficient quality.

A pragmatic quality scoring scheme, using general criteria regarding the date of the study and origin of the data, measurement strategy (e.g. number and type of measurements), information that is reported (e.g. task of workers, information on the validity of the measurement methods) and statistics could be used to distinguish quality levels. Only representative measured data of good quality are considered to be useful for drawing conclusions on exposure levels in Exposure Scenarios based on measurement results only. Measured data of less quality may be used as additional information, e.g. together with model estimates. When there is a wide range of applications, measured data that are used should be tailored to the specific situation. For example, leaching data of a chemical from textile is specific for the chemical and the matrix, and therefore information from one matrix cannot be extrapolated as such to another matrix (and/or chemical). Finally, when obtaining specific measured data, it should be well documented that the associated exposure scenario is indeed realistic worst case.

Exposure models

Workers

To assess worker exposure several types of exposure models exist:

- models based on the physical processes involved, e.g. evaporation, dispersion, dilution; examples: several models made by the US EPA
- statistical models, based on the relation between measured exposure levels and potential determinants of exposure; examples: models often used in epidemiology
- models that categorize determinants in bands and assign exposure levels to resulting bands, often using decision trees; examples: EASE (Tickner et al., 2005) and ECETOC TRA (ECETOC, 2004)
- hybrid models that combine elements of physical process analysis, categorization of determinants and statistical analyses of measured data; examples: RISKOFDERM (Warren et al., 2006) and Stoffenmanager (Marquart et al., 2008, Tielemans et al., 2008)

Most presently used worker exposure models in the scope of regulatory risk assessment are deterministic, *i.e.* they provide a single result for each set of inputs. The models that use decision trees can lead to ranges of exposure for each outcome. RISKOFDERM and Stoffenmanager provide estimates of the exposure levels at percentiles of the expected exposure distribution with each set of inputs. Truly probabilistic worker exposure models would enable the use of probability distributions of input parameters to lead to a probability distribution of the exposure levels. Such models are not yet used in regulatory risk assessments in Europe. A new development is the use of Bayesian models where the results of assessments with prior assumptions can be updated by adding more information or data. An Advanced Worker Exposure Assessment Tool based on this approach is under development.

Consumers

For consumer exposure, in Europe ConsExpo is one of the main models of choice for exposure assessment. ConsExpo provides mathematical exposure models and a defaults database. The mathematical models, which range from screening models to models predicting actual exposure, form the core of the program as they give the dose estimates. The defaults database is set up to provide input to the models. It presents different product categories to the user and provides default parameter values to the models, including justification for the choice of these default values.

ConsExpo allows the user to specify contact (frequency, duration of actual use, duration of contact and start of contact), exposure, and uptake by selecting the appropriate scenarios and models from predefined lists. By combining different models and different exposure routes, the program copes with consumer product diversity. The program allows for stochastic parameters, which can attain three standard distributions, the normal, lognormal and uniform distribution, and thus includes variability and uncertainty. Any value or range of values can be assigned to the different parameters. The program calculates the resulting exposure and uptake distributions, and allows any percentile to be calculated (Delmaar et al., 2005).

Justification of Exposure Based Waiving

Based on exposure scenarios identified in chapter 5 that potentially give reason for EBW, two types of situations can be distinguished which can be treated separately in the process of EBW:

1. Situations which do not require further exposure assessment because it has been agreed that, either or not in combination of knowledge on type of toxicological effect, exposure is very likely too low to require hazard testing.
2. Situations that require exposure models or other methods to indicate that use results in exposure levels below the level of 'no further action' (*i.e.* situation 1 does not apply).

Situation 1 may be decided upon based on the concentration of the substance in a preparation, the amount of substance used, the formulation or packaging of the substance, or certain substance

properties. Specific criteria are needed to ensure that it is reasonable to assume that exposure will remain below the ‘no further action level’ without actually estimating the exposure by modelling. Situation 2 applies to situations where such criteria can not be formulated and an actual exposure estimate is needed to show that exposure is below the level of ‘no further action’. As these levels can be below levels for which methods have been developed, it needs to be determined whether the available models can make a valid estimate of (very) low exposure, while incorporating the relevant parameters of the exposure scenario as identified in chapter 5 with sufficient sensitivity.

5.3.3 Internal exposure

For human exposure, first the external exposure scenario’s should be examined as part of an ITS. When external exposure is estimated to be below the ‘no further action level’ (see section 5.3.2) already EBW of additional tests could be applied. If more information is needed, the kinetics of the compound (especially bioavailability) can refine the exposure estimate to justify EBW.

To recapitulate the general considerations and information given in section 4.3.3, exposure based waiving (EBW) and exposure based triggering (EBT) of tests on the basis of internal exposure is generally based on information gathered by various (testing and non-testing) methods. It should be kept in mind that for compounds under REACH legislation, the elucidation of compound specific kinetics is not required. However, there are opportunities in both experimental testing and modelling to refine the ITS by including kinetics. The assessment of internal exposure can, eventually, result in EBW/EBT. Several considerations are briefly discussed below.

5.3.3.1 Non-testing methods

In general, we need to consider which non-testing methods (including modelling) are possible given the data that we are likely to have. It is assumed that various physicochemical data (e.g. octanol-water partition coefficient, solubility) will be available for each compound. Additional (*in vivo* / *in vitro*) experimental (kinetic) data may exist for some compounds, but in general these data are lacking. The utility of extra data, and examine how such data will contribute to the improvement of the quality of the modelling predictions needs to be considered.

There are few experimental data available in the open literature for industrial chemicals, and it is difficult to see how any developed predictive model may be made suitably robust for these chemicals. It may be necessary to design and validate models using existing data that is available (including data on pharmaceuticals).

Using TTC for internal exposure

Currently it is not clear how the external TTC could be converted to an internal TTC and additional research is needed here.

Using *in silico* approaches

Internal exposure is a complicated function of many parameters. It is necessary to quantify, at minimum, the absorption, distribution and clearance (metabolism and excretion) of a compound.

To go from external to internal exposure, the bioavailability of a compound needs to be estimated. There are three main external exposure scenarios: dermal absorption, pulmonary absorption, and oral absorption. A number of high-throughput assays are used in the pharmaceutical industry to predict oral absorption (PAMPA, Caco-2; see section 5.3.3.2). The utility of these assays for the prediction of the absorption of industrial compounds should be assessed and included in the developed model.

To a certain extent, distribution is driven by lipophilicity, and various lipophilicity-driven distribution models have been proposed in the literature. We should consider which model is most suitable and which measure of lipophilicity is best.

Clearance is a more difficult issue; it can take place by direct elimination, or by metabolism. A number of high-throughput assays are used in the pharmaceutical industry to assess metabolic clearance (microsomal clearance, S9 clearance, hepatocyte clearance), but all have their issues, and none allow the quantitative prediction of *in vivo* metabolism. As for direct elimination, there are currently no widespread assays for biliary clearance, and renal clearance is best modelled as a simple passive process in which the kidneys filter only the unbound compound fraction.

Detailed physiologically-based toxicokinetic (PBTK) models require a great deal of data, and the detailed validation that such models require is likely to cost as many animals as would be saved by their use. However, the generation of such data should be considered as part of other toxicological studies (see section 5.3.3.2). It should be noted that the implementation of REACH presents a considerable opportunity for the development of PBTK modelling. However, the applicability domain of these models for EBW/EBT should be taken into account for each substance.

Generic PBTK models, largely based on lipophilicity, may have some role to play in predicting the toxicokinetics of a parent compound. These predictions should be treated with a certain amount of caution, but the utility of such models is being assessed with reference to a number of studies reported in the scientific literature.

The use of PBTK models for EBW needs further refinement. Criteria are needed for the use of these models. Especially the uncertainty of these models need to be explored before/during application.

5.3.3.2 Testing methods

***In vitro* tests**

To go from external to internal exposure, the bioavailability of a compound needs to be estimated. For dermal absorption, a validated OECD *in vitro* study already exists (OECD 428). Next to dermal absorption, priority should be given to the development of validated *in vitro* studies for oral and inhalatory absorption.

The use of artificial (PAMPA, Parallel Artificial Membrane Permeability Assay) and cell-culture (Caco-2) based membrane models for the prediction of absorption of compounds is based on the assumption that the intestinal epithelium represents the main barrier for compounds to reach the circulation. These membrane models provide a fast, reproducible, simple and relatively cheap method to screen a wide variety of compounds. In addition, *in vitro* test for metabolism can be incorporated in an ITS for EBW (fast metabolic clearance) of EBT (bioactivation of parent compound).

It will be important to implement these *in vitro* test in an ITS. Since these test are not OECD tests, there can be a 'Weight of Evidence' approach for their use in EBW. The validation and incorporation of these *in vitro* methods are out of the scope of the OSIRIS project. The ECVAM (European Centre for the Validation of Alternative Methods) plays an important role in optimization and validation of these required *in vitro* tests. In time, these new developed alternative methods will take their place in an ITS.

(Optimized) *in vivo* tests

An important objective in REACH is the replacement, refinement and reduction in animal experimentation. In this respect, the development of optimized *in vivo* studies for kinetic purposes (not required information under REACH) needs clarification. For new compounds, there are *in vivo* toxicity test requirements, especially in the higher tonnage levels. By including additional (kinetic) endpoints, blood sampling over time and including satellite groups in the OECD protocols, valuable kinetic information can be elucidated for these unknown compounds. This additional kinetic information could result in EBW of further *in vivo* tests and thus a reduction in the amount of animals used.

Guidelines should become available, as an additional option for standard OECD *in vivo* toxicity tests that indicate how additional kinetic information could be obtained.

Furthermore, non OECD *in vivo* test with only a small amount of animals could already provide adequate kinetic information. Especially with these kinetic *in vivo* studies, a ‘Weight of Evidence’ based EBW for internal exposure should be considered. Additional criteria for these *in vivo* studies are needed for application in an ITS.

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ANNEX I: 'Column 2' adaptations for environmental endpoints of Annexes VIII to X

| Endpoint | Protection target | EBW statement | Reference | Comments (RIP 3.3) |
|------------------------------------|---------------------------|--|--------------------------------------|---|
| Bacterial inhibition testing | Activated sludge bacteria | <i>If there is no emission to a sewage treatment plant</i> <i>If the substance is found to be readily biodegradable (+ realistic applied test concentrations)</i> | Annex VIII section 9.1.4 | No explanations in RIP 3.3 |
| Simulation testing surface water | | <i>If the substance is readily biodegradable</i> | Annex IX section 9.2.1.2 | No explanations in RIP 3.3 |
| Simulation testing soil / sediment | | <i>If the substance is readily biodegradable or if direct and indirect exposure of soil/sediment is unlikely</i> | Annex IX section 9.2.1.3 and 9.2.1.4 | No explanations in RIP 3.3 |
| Toxicity testing | Soil organisms | <i>If direct and indirect exposure of the soil compartment is unlikely</i> | Annex IX section 9.4 | Metabolites tend to be less hydrophobic than the parent substance and therefore have a lower adsorption potential, thus the relevance of the metabolites for the sediment compartment is normally lower than for the parent compound. |
| Long term toxicity testing | Soil organisms | <i>If direct and indirect exposure of the soil compartment is unlikely</i> | Annex X section 9.4 | Information on degradation of the parent compound in the water column showing formation of relevant metabolites that will not be distributed to the sediment. Monitoring data showing absence of the substance or relevant metabolites in sediment |
| Bioaccumulation | | <i>If direct and indirect exposure of the aquatic compartment is unlikely</i> | Annex IX section 9.3.2 | Where it can be reliably demonstrated (by measurement or other evidence) that there is no release to the environment at any stage in the life cycle, e.g. a site-limited chemical intermediate. |

| Endpoint | Protection target | REACH EBW/EBT statement | Reference | EBW or EBT | RIP 3.3 Interpretation (+section no.) |
|-------------------------------|-------------------|--|-------------------------|------------|--|
| Skin/eye irritation corrosion | | | | EBW | 7.2.3.3: Exposure-based waiving from testing is not applicable to the endpoints of skin corrosion, skin and eye irritation |
| | | | | | 7.2.6.2: Please note that there is no option for exposure-based waiving for this endpoint in the REACH regulation (see section 7.2.3.3) |
| Acute toxicity | Humans general | In addition to the oral route (8.5.1), for substances other than gases, the information mentioned under 8.5.2 to 8.5.3 shall be provided for at least one other route. | L136/108 Annex VIII 8.5 | EBW | 7.4.3.3: If there is only one demonstrated route of exposure, this route has to be addressed. Where the potential for human exposure exists, the most likely route, or routes, of exposure should be determined so that the potential for acute toxicity by these routes can be assessed. |
| Acute toxicity | Humans general | The choice for the second route will depend on the nature of the substance and the likely route of human exposure. If there is only one route of exposure, information for only that route need be provided. If there is only one route of exposure, information for only that route need be provided. | Idem | | Determination of the most likely route of exposure will not only have to take into account how the substance is manufactured and handled, including engineering controls that are in place to limit exposure, but also the physico-chemical properties of the substance |
| Acute toxicity | | | Idem | | At the tonnage level of 10 tpa and above (annex VIII), data on oral acute toxicity should be provided, unless the substance is a gas or volatile liquid. In this case, acute toxicity information should be provided for the dermal or inhalation route depending on the physical properties of the substance and the anticipated human exposures. |

| Endpoint | Protection target | REACH EBW/EBT statement | Reference | EBW or EBT | RIP 3.3 Interpretation (+section no.) |
|------------------------|---------------------------|---|--------------------------------------|-------------------------------|---|
| Repeated dose toxicity | Humans general | The short-term toxicity study (28 days) does not need to be conducted if: -relevant human exposure can be excluded in accordance with Annex XI, section 3. | L136/108 Annex VIII 8.6.1 | EBW | Relevant human exposure depends on the inherent properties of the substance, if the population comes into contact with the substance or not, and how the substance is used. Thus, waiving might be considered on a case-by-case basis. |
| Repeated dose toxicity | Humans general | The sub-chronic toxicity study (90 days) (Annex IX, Section 8.6.2) shall be proposed by the registrant if: - the frequency and duration of human exposure indicates that a longer term study is appropriate; and ... 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. | L136/108 - L136/109 Annex VIII 8.6.1 | EBT (incl. internal exposure) | |
| Repeated dose toxicity | Humans general & consumer | Further studies shall be proposed by the registrant or may be required by the Agency in accordance with Article 40 or 41 in case of: - the route of exposure 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. - particular concern regarding exposure (e.g. use in consumer products leading to exposure levels which are close to the dose levels at which toxicity to humans may be expected) | Idem | EBT | RIP3.3 According to Annex VIII-X further studies shall be proposed by the registrant or may be required by the agency for example if there is particular concern regarding exposure, e.g. use in consumer products leading to exposure levels which are: - close to the dose levels at which toxicity to humans may be expected (Annex VIII) i.e. a dose lower than, but in the vicinity of, the dose levels at which toxicity to humans may be expected - high relative to [NB: REACH says close to] the dose levels at which toxicity to human may be |

| Endpoint | Protection target | REACH EBW/EBT statement | Reference | EBW or EBT | RIP 3.3 Interpretation (+section no.) |
|------------------------|-------------------|--|--|-------------------------------|--|
| | | | | | <p>expected (Annex IX) i.e. exposure levels higher than the dose levels at which toxicity to humans may be expected</p> <p>- close to the dose levels at which toxicity is observed (Annex X) i.e. a dose lower than but in the vicinity of the dose levels at which toxicity is observed from animal studies.</p> <p>Any of the exposure -triggered studies proposed by the registrant or required by the agency should be considered on a case-by-case basis</p> |
| Repeated dose toxicity | Humans general | <p>The sub-chronic toxicity study (90 days) does not need to be conducted if:</p> <ul style="list-style-type: none"> - the substance is unreactive, insoluble 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. | L136/112 Annex IX 8.6.2 | EBW (incl. internal exposure) | <p>In order to omit the study, the prerequisites interpreted above have to be considered jointly since the word 'and' is used in between them. In addition, limited human exposure would strengthen the possibility for waiving. The interpretation of 'un-reactive' can be that it relates to inherent chemical reactivity and as such, is an indicator of lack of local effects and mutagenicity, 'insoluble and not inhalable' can be interpreted as indicators of low exposure potential and should be further defined, and 'no evidence of absorption' that there has to be evidence for lack of absorption in order to omit the study.</p> <p>Further 'no evidence of toxicity in a 28-days limit test' can be interpreted as it has to be at least a 28-days limit test available in order to waive the 90-days study, and this 28-days study should not show any sign of toxicity at 1000 mg/kg.</p> |
| Repeated dose toxicity | Consumer | <p>Further studies shall be proposed by the registrant or may be required by the Agency in accordance with Articles 40 or 41 in case of:</p> <ul style="list-style-type: none"> - particular concern regarding exposure (e.g. use in consumer products leading to exposure levels which are close to the dose levels at | L136/113 Annex IX 8.6.2 & L136/117 Annex X 8.6.4. | EBT | |

| Endpoint | Protection target | REACH EBW/EBT statement | Reference | EBW or EBT | RIP 3.3 Interpretation (+section no.) |
|------------------------|-------------------|---|--|------------|---|
| | | which toxicity to humans may be expected). | | | |
| Repeated dose toxicity | Humans general | <p>A long-term repeated toxicity study (≥ 12 months) may be proposed by the registrant or required by the Agency in accordance with Articles 40 or 41 if the frequency and duration of human exposure indicates that a longer term study is appropriate and one of the following conditions are met:</p> <ul style="list-style-type: none"> - serious or severe toxicity effects of particular concern - effects shown in substances with a clear relationship in molecular structure were not detected in the 28-day or 90-day study - the substance may have a dangerous property that cannot be detected in a 90-day study | L136/117 Annex X 8.6.3 | EBT | |
| | | | | | |
| Reproductive toxicity | Humans general | <p>This study does not need to be conducted if:</p> <ul style="list-style-type: none"> - the substance is known to be a genotoxic carcinogen and appropriate risk management measures are implemented, or - the substance is known to be germ cell mutagen and appropriate risk management measures are implemented, or - relevant human exposure can be excluded in accordance with Annex XI section 3 (VIII) - the substance is of low toxicological activity, it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure and there is no significant human exposure (IX and X) | L136/109 Annex VIII 8.7.1 & L136/113 Annex IX 8.7 & L136/117 Annex X 8.7 | EBW | 7.6.6.2: However, regardless of tonnage level, before any testing is triggered, careful consideration of all the available toxicological data, exposure characteristics and current risk management procedures is necessary to ascertain whether the fundamental objectives of the ITS (see above) have already been met. |
| Reproductive | | | Idem | | 7.6.6.3 Stage 1.2: Is the substance classified as a genotoxic carcinogen (Carcinogen Category 1 |

| Endpoint | Protection target | REACH EBW/EBT statement | Reference | EBW or EBT | RIP 3.3 Interpretation (+section no.) |
|-----------------------|-------------------|-------------------------|-----------|------------|---|
| toxicity | | | | | <p>and Mutagen Category 3 or Carcinogen Category 2 and Mutagen Category 3) or a germ cell mutagen (Mut. Cat. 1 or Cat. 2)?</p> <p>If the answer is no, proceed to Stage 1.3. If the answer is yes, it is important to establish that appropriate risk management measures addressing potential carcinogenicity, genotoxicity and reproductive toxicity have been implemented and therefore further specific testing for reproductive and/or developmental toxicity will not be necessary. Exceptionally, appropriate risk management measures may not be in place and a Stage 2 review of the available data should be considered.</p> |
| Reproductive toxicity | | | Idem | | <p><i>Upgraded testing requirements</i></p> <p>The use pattern or the exposures to a substance may indicate a need for additional information requirements, on a case-by-case basis. For example, there may be serious concerns that human exposures, particularly to consumers, are close to the levels at which toxicity might be expected. Such concerns for human health may be satisfactorily addressed by improved risk management measures and therefore additional information on hazard would be of limited value. Thus, proposals to refine a risk assessment with the use of information obtained from new <i>in vivo</i> testing that is in excess of the REACH tonnage-related information requirements can be justified only in exceptional circumstances.</p> |
| Reproductive toxicity | | | Idem | | <p><i>Reduced testing requirements: $\geq 10 \text{ tpa}$</i></p> <p>As stated in REACH Annex VIII specific rules for adaptation the OECD TG 421/422 study listed as a standard information requirement does not</p> |

| Endpoint | Protection target | REACH EBW/EBT statement | Reference | EBW or EBT | RIP 3.3 Interpretation (+section no.) |
|-----------------------|-------------------|-------------------------|-----------|------------|--|
| | | | | | need to be conducted if relevant human exposure can be excluded in accordance with Annex XI section 3. This clause states that tests may be omitted based on exposure scenarios developed in the Chemical Safety Report. The criteria defining what constitutes adequate justification for omitting these tests under Annex XI section 3 are not currently available, but will be adopted by the Commission within 18 months of REACH coming into force. |
| Reproductive toxicity | | | Idem | | 7.6.2: Factors that can influence the testing requirements include structural relationships with other chemicals, the results of other toxicity studies, presence of mutagenic and carcinogenic properties, available data from humans exposed to the substance, concerns for endocrine disruption and the use and human exposure patterns . |
| Reproductive toxicity | | | Idem | | 7.6.3.3: General information on the pattern and extent of human exposure to the substance must be considered, as this may influence the data requirements with respect to reproductive toxicity. |
| Reproductive toxicity | | | Idem | | 7.6.4.3: Generic aspects of data waivers based on exposure considerations are presented in chapter 5.1.3. There are rules for waiving certain reproductive information requirements that include criteria relating to human exposure levels in REACH Annexes IX and X. Furthermore, all the reproductive toxicity tests (and also most |

| Endpoint | Protection target | REACH EBW/EBT statement | Reference | EBW or EBT | RIP 3.3 Interpretation (+section no.) |
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| | | | | | other <i>in vivo</i> toxicity) may be omitted at any of the tonnage levels based on exposure scenarios developed in the Chemical Safety Report according to REACH Annex XI section 3. The influence of human exposure on the reproductive toxicity ITS is discussed in more detail in section 7.6.6. |
| Reproductive toxicity | | | Idem | | 7.6.6.4: As part of the Stage 2 data review the following questions should be asked: if the data are insufficient, what study (or studies) is most appropriate? This decision must take account of both the standard tonnage related information requirements of REACH, the nature of the alert(s) and Weight of Evidence as well as human exposure considerations . |
| Reproductive toxicity | | | Idem | | 7.6.6.5 (The Whole Section!!!) Exposure considerations may be used to justify the waiver of certain data requirements or, exceptionally, the conduct of reproductive toxicity testing that is additional to the REACH Annex VIII, IX and X information requirements. |
| Reproductive toxicity | | | Idem | | In addition to the REACH Annex IX and X specific rules for adaptation, there is the parallel exposure-based provision in Annex XI section 3 of the REACH Regulation (Substance tailored exposure-driven testing); All the reproductive toxicity tests (and also most other <i>in vivo</i> toxicity) may be omitted at any of the tonnage levels based on exposure scenarios developed in the Chemical Safety Report. As stated above, the criteria defining what constitutes |

| Endpoint | Protection target | REACH EBW/EBT statement | Reference | EBW or EBT | RIP 3.3 Interpretation (+section no.) |
|-----------------------|-------------------|---|--|-------------------------------|---|
| | | | | | adequate justification for omitting these tests under section 3 are not currently available. |
| Reproductive toxicity | | The studies do not need to be conducted if: - the substance is of low toxicological activity (no evidence of systemic toxicity seen in any of the tests available), it can be proven from toxicokinetic data that <i>no</i> 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 there is no or no significant human exposure. | L136/113 Annex IX 8.7 & L136/117 Annex X 8.7 | EBW (incl. internal exposure) | <p>7.6.6.3 Stage 1.3 Does the substance exhibit (a) low toxicological activity and (b) <i>negligible</i> systemic absorption and (c) no or no significant human exposure?</p> <p>At the ≥ 100 and ≥ 1000 tpa levels, no further testing for reproductive toxicity will be required if all three criteria (a, b and c, above) are met; otherwise proceed to the stage 2 analysis. In addition, testing will not be required if the application of a parallel exposure-based information waiving provision in Annex XI section 3 of REACH (Substance-tailored exposure driven testing) is justified. However, these three criteria do not apply at the >10 tpa level. At this level, no further testing for reproductive toxicity will be necessary only if the application of the exposure-based information waiving provision in Annex XI section 3 of REACH is justified; otherwise proceed to the stage 2 analysis.</p> |
| Reproductive toxicity | | | Idem | | <p><i>Reduced testing requirements: ≥ 100 tpa and ≥ 1000 tpa</i></p> <p>According the REACH Annex IX and X specific rules for adaptation (mainly column 2), the reproductive toxicity studies listed as standard information requirements do not need to be conducted if the three following criteria are met:</p> <ol style="list-style-type: none"> 1. The substance is of low toxicological activity (no evidence of toxicity seen in any of the tests |

| Endpoint | Protection target | REACH EBW/EBT statement | Reference | EBW or EBT | RIP 3.3 Interpretation (+section no.) |
|-----------------|-------------------|---|------------------------------|------------|--|
| | | | | | <p>available) and</p> <p>2. 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</p> <p>3. There is no or no significant human exposure. At least two cases pertain, the first being no human exposure (e.g., substances only produced and used in closed systems) and the second being no significant human exposure. Whether a human exposure is significant depends on the reproductive toxicity potency of the substance relative to exposure (consequence of a risk) and might be decided on the basis of other information indicating e.g. the probability of a risk. E.g.: At least substances used in closed systems fall under this criterion, but other possibilities may be identified as well e.g. industrial and commercial uses for substances exclusively used in preparations in very low concentrations or substances, uses of substances in consumer products which are completely chemically reacted during manufacturing, integrated in a matrix and characterized by very low migration.</p> |
| Carcinogenicity | Humans general | <p>A carcinogenicity study may be proposed by the registrant or may be required by the Agency in accordance with Articles 40 or 41 if:</p> <ul style="list-style-type: none"> - the substance has a widespread dispersive use or there is evidence of frequent or long-term human exposure | L136/117 Annex X 8.9.1 | EBT | <p>7.7.13.3b A carcinogenicity study may, on occasion, be justified. If there are clear suspicions that the substance may be carcinogenic, and available information (from both testing and non-testing data) are not conclusive in this, both in terms of hazard and potency, then the need for a carcinogenicity study should be explored. In</p> |

| Endpoint | Protection target | REACH EBW/EBT statement | Reference | EBW or EBT | RIP 3.3 Interpretation (+section no.) |
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| | | | | | particular, such a study may be required for substances with a widespread, dispersive use or for substances producing frequent or long-term human exposures. However, it should be considered only as a last resort. |
| Carcino- genicity | | | Idem | | On the other hand, investigations on the carcinogenic properties of a chemical can be deferred, if it can be demonstrated to the satisfaction of the Agency that the chemical is used only in a closed system and that human exposures are negligible, (i.e. risk reduction measures on the substance are already equivalent to those applied to high potency carcinogenic substances of category 1 and 2. Reasons for this could include the presence of other substances for which strict exposure regimes are implemented or enforced). The rationale for exemption from testing, of course, needs to be clearly documented upon registration. |
| Carcino- genicity | | | Idem | | 7.7.11.4 Finally, conventional assays of carcinogenicity in animals have been found to be insensitive for some well-established human carcinogenic substances (e.g. asbestos and arsenic compounds). These substances can be shown to be carcinogenic when the test conditions are modified, thus illustrating that there will always be a possibility that a chemical could pose a carcinogenic hazard in humans but be missed in conventional animal studies. This is also true for other toxicological endpoints and should be taken into account by risk managers, especially when |

| Endpoint | Protection target | REACH EBW/EBT statement | Reference | EBW or EBT | RIP 3.3 Interpretation (+section no.) |
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| | | | | | making decisions about the acceptability of scenarios showing particularly high exposures to workers and/or consumers. |
| Carcino- genicity | | | Idem | | If no conclusion can be drawn regarding the potential genotoxicity of the substance then, in general, it will be determined on a, case-by-case basis when and how the carcinogenic potential should be explored further. Again, this will then depend on the type and strength of the indications for carcinogenicity, the potential mechanism(s) of action, and the type and level of human exposure. |
| Carcino- genicity | | | Idem | | 7.7.13.2 On very rare occasions, a case may be made to perform a carcinogenicity study in animals for substances that have been classified for mutagenicity in categories 1 or 2. Such a case would have to explain why the study was critically important; e.g. in the context of the clarification of carcinogenic risk associated with human exposures. |
| Carcino- genicity | | | Idem | | For substances at the REACH Annex X tonnage level, the need for or waiving of a standard animal test should be clearly explained, taking into account all the available toxicological and hygiene information on the substance and/or other relevant substances. For example, if it can be demonstrated that the substance is used only in a closed system and that human exposures are negligible, it is possible to propose no further testing for carcinogenicity. |

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