

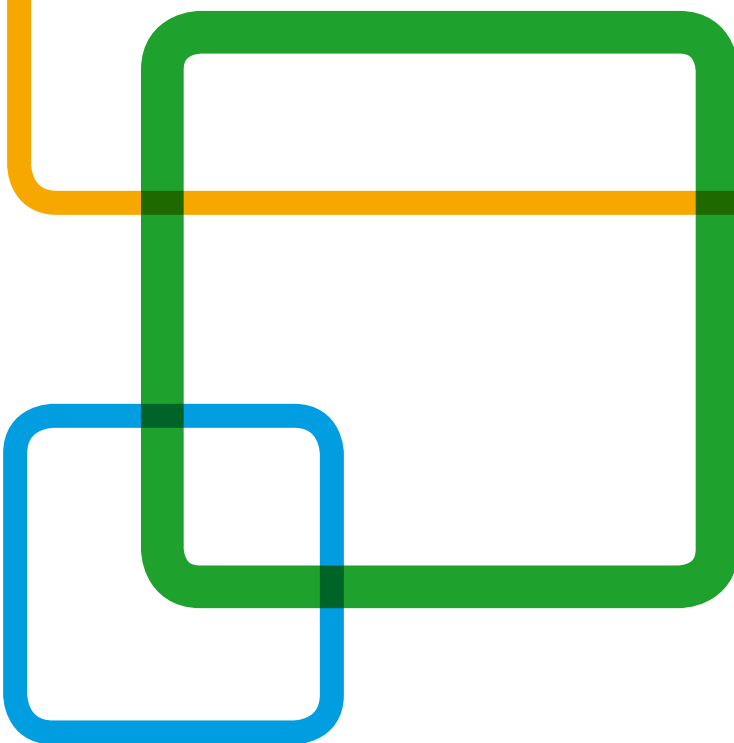


Global Product Strategy

ICCA Guidance on Chemical Risk Assessment

Product Stewardship in action:

Sound chemicals management is a global responsibility



DISCLAIMER

The document at hand does not attempt to present legally binding requirements but outlines the steps viewed as necessary to perform risk assessments as envisioned under the ICCA GPS initiative. A particular risk assessment practice described in this document may not apply to an individual situation based upon the circumstances. Interested parties are free to raise questions and objections about the chemical or the practices discussed in this document and the propriety nature of the application of those practices to a particular situation.

Any individual or site-specific risk management decision will be based on the applicable statute and regulations, and on facts specific to the circumstances at issue. Variance from the approaches outlined in this document does not necessarily have any significance. Decision makers retain the discretion to adopt approaches on a case-by-case basis that differ from those described in this document where appropriate. Risk assessments discussed in this guidance paper reflect a “snapshot” in time and may not be reflective of any further assessment activity past the time of a particular description. Users are reminded that the information in this document constitutes neither legal nor mandatory advice.

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INTRODUCTION

The Global Product Strategy (GPS) was developed by the International Council of Chemical Associations (ICCA) as part of its commitment to the United Nations Strategic Approach to International Chemicals Management program.

GPS is part of the international chemical industry's voluntary Responsible Care Global Charter¹. It commits companies to promote the safe use of chemical products and enhance product stewardship throughout the value chain. GPS is a capacity-sharing exercise working towards:

- Reducing differences in the safe handling of chemical substances between developing, emerging and industrialized countries.
- Ensuring the correct handling and use of chemicals across the value chain and across geographical boundaries by providing relevant and reliable information.
- Greater transparency, by helping companies provide stakeholders with information about marketed chemicals in an easily understandable format: the GPS Safety Summary.

Background

This document has been produced for developing regions and small and medium-sized companies. It is intended as a “living document” to be improved over time, based on feedback received from companies who use it.

The document is part of a series of guidance documents to help ICCA member companies fulfill their commitment to perform risk assessment under GPS, define safe use conditions and if necessary, implement risk management measures so that safe use conditions are met².

Purpose

By this GPS step-by-step process, companies with limited experience and resources will master basic principles, enabling them to implement appropriate risk assessment and risk management.

Because the processes described here is aligned with internationally recognized programs such as the High Production Volume (HPV) chemicals program, companies implementing the GPS system will get closer towards implementing complex international standards.

How to use this document

Follow Consecutive Steps: The document is divided into two main sections – each comprising of four individual steps. Section One is the “preparation” phase. It shows the reader, step-by-step how to gather the information needed in order to conduct the risk assessment. Section Two is the “implementation” phase. Here the reader is shown how to perform the risk assessment.

The completion of each step prepares the reader for the next step therefore it is important to address each step in the right order. Page 7 summarizes the entire step-wise process.

Where needed, each Step is extended with a Supplement in order to provide the background or added detail required in order to complete the step. A glossary of terms and a list of references are provided at the end of the document.

INTRODUCTION

The GPS Risk Assessment System Basic Principles of Risk Assessment

A very important concept is the distinction between hazard and risk. Hazard defines the inherent property of a chemical having the potential to cause adverse effects when an organism, system or population is exposed to that agent. Risk however, establishes the probability of the adverse effect occurring. Risk Assessment leads to a thorough understanding of the nature, magnitude and probability of a potential adverse health or environmental effect of a chemical. It addresses uncertainties around hazard and exposure.

Risk assessment should be conducted by experts who have knowledge about the intrinsic properties of the chemicals and the context in which the substances are used, and the control options available to manage risk.

Several risk assessment methods exist, particularly for complex circumstances. See Annex 1, pages 145 for more information. The GPS system described in this document follows best practice international principles and is based upon the following basic steps:

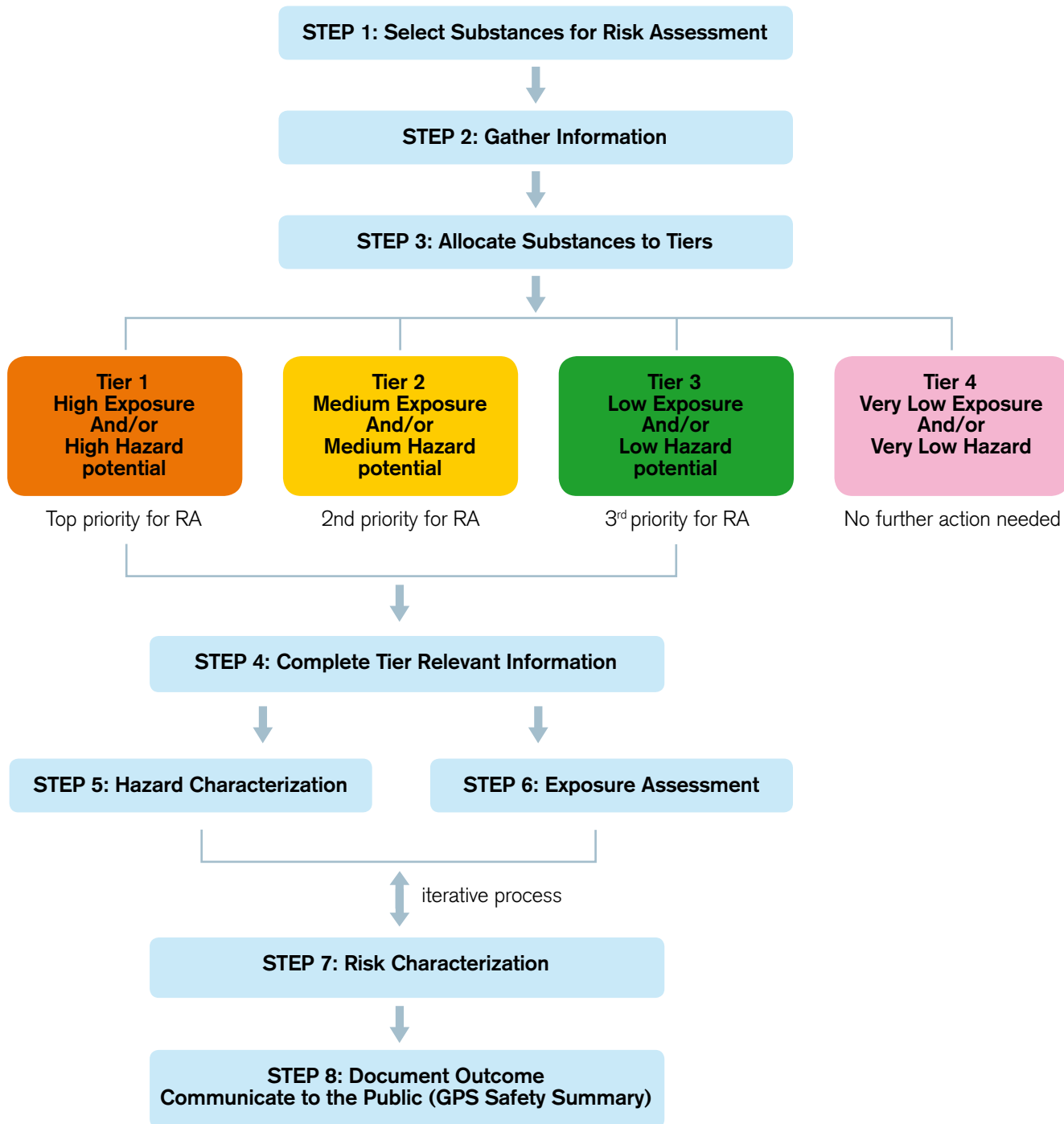
Hazard characterization: dose-response determination, determining the relationship between the magnitude of exposure to a hazard and the probability and severity of adverse effects, (see page 43)

Exposure assessment: identifying the extent to which exposure actually occurs (see page 88)

Risk characterization: combining the information from the hazard characterization and the exposure assessment in order to form a conclusion about the nature and magnitude of risk, and, if indicated, implement additional risk management measures (see page 114). Risk characterization is an iterative process. There might be several circles of assessment necessary before you can conclude that the substance can be handled safely.

The chart below summarizes the eight steps of the GPS Risk Assessment process.

Figure 1: The GPS Risk Assessment Process



SECTION ONE PREPARATION

This section leads companies through the preparation stage of information gathering in four individual steps. By the end of Section One, the reader will have allocated chemicals into priority Tiers for risk assessment and gathered the appropriate level of information needed to conduct the risk assessment of each chemical.

Box 1: Preparation needed in order to be able to conduct the GPS Risk Assessment

STEP 1: Select substances for the GPS Risk Assessment

STEP 2: Gather all available information on all chemicals entering the GPS risk assessment process

STEP 3: Based on the results of Step 2, allocate chemicals into Tiers in order to prioritize them for risk assessment

STEP 4: Develop Tier-relevant information in order to ensure the appropriate level of information (Base Set Tier) in order to be able to conduct the risk assessment process outlined in Section Two

Address priority chemicals in priority

An important concept of this section is the prioritization of chemicals into groups or “Tiers” according to an initial consideration of their hazard and / or exposure potential. Each Tier is associated with a set of information needed for risk assessment. Chemicals with higher hazard and / or exposure potential (e.g. those allocated to Tier 1) would be risk assessed first. These chemicals also need more information as a starting point for their risk assessment than chemicals with lower hazard or exposure potential (e.g. Tier 4).

PLEASE NOTE:

- (1) Just because a chemical is allocated to Tier 1: priority for risk assessment – this does not mean that the risk assessment outcome will show the chemical is of highest risk. Risk is a combination of hazard and exposure as described in Section Two. In Section Two we will see that by implementing appropriate risk management measures, even a hazardous substance can be safely used in accepted applications.
- (2) The level of technical guidance in this document is intended to be simple and pragmatic: a first step for beginners in risk management. Detailed technical guidance can be obtained from other sources (see Annex 1, page 145).
- (3) Conducting risk assessments on mixtures of chemicals is an issue to be addressed in a later addition to this document, based on the experience of new regulatory programs such as REACH. In the meantime, and in the absence of globally accepted risk assessment methods for mixtures, GPS recommends the following approach: *the risk of the mixture or product should be assessed based on the risk of the most hazardous ingredient.*

SECTION ONE PREPARATION

STEP 1: SELECT SUBSTANCES FOR GPS RISK ASSESSMENT

In Step 1 you will:

- First, make an inventory* of the chemicals your company sells into the market or transports off the production site.
- Second, establish whether there are any exemptions to the risk assessment.

Box 2: Substances falling under the GPS Risk Assessment System

GPS risk assessments should be performed for chemicals that

- Are sold (“in commerce”) or transported world-wide in quantities of more than 1 metric ton per year by company and those that
- Pose a major threat to human health and/or the environment (e.g. known carcinogens, reproductive hazards, extremely toxic, persistent and bioaccumulating) - even if they are sold or transported in smaller amounts than 1 metric ton per year.

Exemptions: chemicals for which Risk Assessments do *not* need to be performed

- Chemicals that are Active Pharmaceutical Ingredients (APIs)
- Chemicals not used as industrial chemicals and therefore already covered under specific regulations (e.g. agricultural active ingredients, biocides, cosmetics or food & feed applications)
- Chemicals used for military purposes (e.g. explosives)
- Non-isolated, non-transported intermediates
- Isolated on-site used intermediates under strictly controlled conditions
- R&D chemicals
- Waste and or recycling of products

* The inventory should be kept strictly company internal due to antitrust / competition law compliance. DO NOT discuss chemicals on this list with other companies. For more information on antitrust / competition law compliance, please refer to: [Antitrust and competition law guide for ICCA Members](#).

STEP 2: GATHER INFORMATION

In Step 1 you made an inventory of all the chemicals to go through the GPS risk assessment. In Step 2 you will be shown how to gather available information on each chemical in order to be able to judge its priority for the subsequent risk assessment:

In Step 2 you are shown how to gather 3 separate types of information:

- **Standard Parameters:** the same for all chemicals, regardless of hazard
- **Hazard Information:** intrinsic information for each substance based on pre-defined health and environment end points.
- **Exposure Information:** unique to each application / use and each company. Based on exposure categories and dependent on use

PLEASE NOTE: Prior to embarking on Step 2, first take time to consider the following:

- (1) **How to obtain the information:** in order to gather the information required, first check your company's internal databases and gather existing hazard and exposure information on your chemical substances. Next, refer to Table 2, page 16 in order to identify the major information sources to access more information on your chemicals (standard parameters, hazard and exposure information). In most cases, the information is publicly available and free of charge.
- (2) **Evaluate the quality of the Information:** whenever possible, always favor high-quality information sources. Certain sources of information are more favorable than others in terms of quality, reliability, relevance and accuracy of findings. For example, data generated with OECD Test Guidelines in compliance with OECD GLP are recognized as of highest quality and accepted in most countries³. For more information on how to assess whether the information is reliable, see page 20 and refer to the Klimisch code⁴ or US EPA criteria⁵:
- (3) **Data Gaps:** If, by the end of Step 2 you find gaps in the information gathered from publicly available sources, you may need to generate the remaining information from alternative sources. This "gap filling" exercise - should it be necessary - is explained in Step 3.

SECTION ONE PREPARATION

STEP 2: GATHER INFORMATION

Standard Parameters

Standard parameters must be developed for all the chemicals selected for risk assessment. They consist of the chemical's identity, its physical/chemical properties; toxicity, ecotoxicity and biodegradability as shown in Table 1 below. You will find a list of the sources for this information on pages 16-19.

Table 1: Standard Parameters of Chemical Substances

| Standard Parameter | Description |
|--|--|
| Chemical Identity and use | <ul style="list-style-type: none">• CAS Number(s)• Name• Structural Formula• Composition of the chemical(s) being assessed. In cases where confidentiality issues are involved, the values can be reported in ranges): For a single chemical: degree of purity, known impurities or additives, details of stereo-isomers if relevant.• Use Pattern (categories and types of use)• Sources of Exposure: Is there potential for human exposure to the chemical for example via occupational exposure, consumer exposure and indirect exposure of man via the environment (companies are not requested to provide proprietary information).• Route of Exposure (route of expected human intake): inhalation, dermal, oral for human exposure. |
| Classification and labeling information | <ul style="list-style-type: none">• Physical hazard; Health hazard; Environmental hazard |
| Physical-Chemical Properties | <ul style="list-style-type: none">• Physical State• Melting Point• Boiling Point• Relative Density (required for inorganic chemicals, and should be provided if readily available for organic chemicals)• Vapour Pressure• Partition Co-efficient: n-Octanol/Water• Water Solubility• Ignition Temperature (Flammability) |
| Environmental Fate | Aerobic biodegradability |
| Environmental Toxicology | Acute Toxicity (fish or daphnia) |
| Mammalian Toxicology | Acute Toxicity required only on the most relevant route of exposure (route of exposure that most resembles the route of expected human intake) either by oral route, dermal route or inhalation). In most cases the ambient physical state of the chemical will determine the relevant exposure. |

Hazard Information

As a starting point gather all available information (in house and online) on the hazard endpoints listed below. For a list of information sources, see page 16. The range of information sources can vary widely, including reliable information from supplier (Material) Safety Data Sheets and labels, classification and labeling information, published reports. Companies should use information already completed under other programs such as REACH, GHS, OECD SIDS, HPV, or the EPA IUR. Based on this information, you will later be able to compare the level of intrinsic hazard properties of the chemical and prioritize it for assessment (see page 7).

The ICCA GPS approach does not always demand the availability of animal test data – as long as the information is considered reliable, alternative sources are accepted (see page 38). It is essential that sufficient reliable information is available to enable the implementation of each step of the GPS system. The quality and credibility of the risk assessment is dependent upon the reliability of the information used in the risk assessment process.

Box 3: Hazard Endpoints

Human Health

- Acute toxicity (skin / oral inhalation)
- Eye / Skin irritation and corrosivity
- Sensitization
- Mutagenicity / Carcinogenicity
- Repeated dose (skin / oral / inhalation)
- Reproductive or Developmental toxicity (skin / oral / inhalation)

Environment

- Acute toxicity
- Chronic toxicity
- Persistence
- Bioaccumulation

Physical-chemical hazards

- Flammability (GHS classification)
- Reactivity

SECTION ONE PREPARATION

STEP 2: GATHER INFORMATION

Exposure Information

Exposure is a determinant of the effect of chemicals on humans and the environment - an important factor in risk assessment. Exposure is defined as contact over time and space between a person and one or more biological, chemical or physical agents⁶.

The potential for exposure depends on the “use” of the chemical (e.g. processing, formulation, mixing, filling, and production of a consumer product) which could lead to human or environmental exposure.

The “safe use of chemicals” is the fundamental aim. One important step to achieve safe use is to assess all potential exposures (see page 88 for more information).

As with hazard information, start by gathering all the available information (in house and online) on the exposure conditions of the chemical listed in Box 4 below. You will find a list of the sources for external information on page 18. Based on this information, you will be able to assign potential for exposure of the chemical and prioritize it for assessment (see page 26).

Gather information on the following areas (see page 88 for more information).

Box 4: Exposure Conditions

- Product Characteristics (e.g. volume used in different sectors, packaging)
- Product uses (e.g. transported isolated intermediate used/stored off site; chemical included into or onto a matrix, non-dispersive use, professional industry point sources, wide dispersive use).
- Operational Conditions and Risk Management Measures (e.g. process conditions protective equipment, ventilation, typical handling)
- Environmental Characteristics (e.g. surrounding environment, waste water treatment, typical sector info from ERC or SPERCs)

Table 2: Sources of information

| GHS Classification Databases | |
|---|---|
| Change text in left hand column to: GHS | http://ec.europa.eu/enterprise/sectors/chemicals/classification/index_en.htm |

| Sources for Phys.-Chem Information | |
|--|--|
| Beilstein Database | www.stn-international.com/beilstein_substance.html?&L=0&cHash= |
| CRC Handbook of Chemistry and Physics | www.hbcnetbase.com/ |
| Illustrated Handbooks of Physico-Chemical Properties and Environmental Fate for Organic Chemicals. | www.cababstractsplus.org/abstracts/Abstract.aspx?AcNo=19982303489 |
| IUPAC Solubility Data Series | http://old.iupac.org/publications/sds/index.html |
| The Merck Index | http://library.dialog.com/bluesheets/html/bl0304.html |

| Sources for Hazard Information | |
|---|--|
| Concise International Chemicals Assessment Document (CICAD) | www.inchem.org/pages/cicads.html |
| Database expected to be made public by REACH/CL | Under development |
| ESIS/ORATS of the former ECB (European Chemicals Bureau) | http://ecb.jrc.ec.europa.eu/esis/index.php?PGM=ora |
| European Occupational Exposure Limits (OEL) | http://osha.europa.eu/en/topics/ds/oel/ http://osha.europa.eu/en/publications/reports/OELs_table/view |
| HSDB | http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB |
| ICCA High Production Volume (HPV) assessment dossiers | http://webnet.oecd.org/hpv/ui/Default.aspx |
| OECD eChem Portal | http://webnet3.oecd.org/echemportal/ParticipatingDb.aspx |

Sources for Hazard Information (cont)

| | |
|---|--|
| International Agency for Research on Cancer (IARC) Publications | www.iarc.fr/en/publications/index.php |
| IPCS Concise International Chemical Assessment Documents (CICADs) | www.inchem.org/pages/cicads.html www.inchem.org/ |
| Japanese initial risk assessment reports of chemical substances | www.safe.nite.go.jp/risk/riskhykd101.html |
| Material Safety Data Sheets (check reliability) | www.eusdb.de/en |
| National Institute of Advanced Industrial Science And Technology, Risk Assessment Documents | http://unit.aist.go.jp/riss/crm/mainmenu/1.html |
| NITE CHRIP | www.safe.nite.go.jp/japan/db.html |
| NTP CERHR Publications and Study Reports | http://cerhr.niehs.nih.gov/reports/index.html http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm |
| OECD eChemPortal | http://webnet3.oecd.org/echemportal |
| ORATS (Online European Risk Assessment Tracking System) ESIS (European Chemical Substance Information System) | http://ecb.jrc.ec.europa.eu/esis/index.php?PGM=ora http://ecb.jrc.ec.europa.eu/esis/ |
| Recommendation of Occupational Exposure Limits issued by Japan Society for Occupational Health | http://joh.med.uoeh-u.ac.jp/oel/index.html |
| The Toxic Substance Control Act Test Submission Database | www.syrres.com/esc/tscats.htm |
| Threshold Limit Values of ACGIH (fee required) | www.acgih.org/store/ |
| US EPA Integrated Risk Information System (IRIS) Toxics Release Inventory (TRI) ECOTOX Database Risk assessment portal | http://www.epa.gov/iris/ http://www.epa.gov/enviro/html/tris/tris_query.html www.epa.gov/ecotox www.epa.gov/risk/guidance.htm |
| Working Environment Evaluation Standards under Industrial Safety and Health Act | www.jaish.gr.jp/anzen/hor/hombun/hor1-18/hor1-18-2-1-0.htm |

Sources for Exposure Information

| | |
|---|---|
| A.I.S.E.: (International Association for Soaps, Detergents and Maintenance Products) | www.aise.eu/reach/exposureass_sub2.htm |
| CEPE coatings, inks & artists' colours manufacture and application | www.cepe.org/EPUB/easnet.dll/ExecReq/Page?eas:template_im=100087&eas:dat_im=101AED |
| Chemical Safety Assessment and Reporting Tool (Chesar) | <p>The European Chemicals Agency has developed and Chemicals Exposure and Safety Assessment Reporting tool (CHESAR) for REACH. The Chesar tool uses the ECETOC TRA as the default exposure tool, but the results of other estimating tools or measured data can be used as well. The tool will be further developed over the next years and it can be downloaded from the IUCLID download website:</p> <p>http://echa.europa.eu/reach/software/iuclid5_en.asp</p> |
| Deutsche Bauchemie (German Construction Chemicals) | http://info.vci.de/user_cc/default.aspx |
| Emission scenario documents published by OECD | www.oecd.org/document/46/0,3343,en_2649_34373_2412462_1_1_1_1,00.html |
| EMKG-EXPO-TOOL | <p>The EMKG-EXPO-TOOL is part of the "Easy-to-use workplace control scheme for hazardous substances" (EMKG "Einfaches Maßnahmenkonzept für Gefahrstoffe") of the Federal Institute for Occupational Safety and Health (BAuA). Within the context of REACH the BAuA-Unit 4.1 - Occupational Exposure- offers an IT-tool free of charge for a first exposure estimate at the workplace. This Tier 1 assessment is only valid for inhalation exposure.</p> <p>www.reach-clp-helpdesk.de/reach/en/Exposure/Exposure.html</p> |

Sources for Exposure Information (cont)

| | |
|---|---|
| <p>Generic Exposure Scenarios (GES)</p> | <p>GES describe exposure assessments for (groups of) substances for an area of operation within industry including Risk Management Measures & Operational Conditions relevant for safe use of a group of substances with a similar risk profile.</p> <p>http://cefic.org/en/reach-for-industries-libraries.html</p> |
| <p>Sector groups have developed use descriptors typical for their sector</p> | <p>This gives overview of links to different sectors with their use mappings</p> <p>http://cefic.org/en/reach-for-industries-libraries.html</p> |
| <p>Specific Environmental Release Classes (SPERCs)</p> | <p>Describe the typical operations in their sectors including (conservative) release factors and efficiencies of RMM/OC.</p> <p>http://cefic.org/templates/shwPublications.asp?HID=750&T=806</p> |
| <p>Occupational Exposure to Hazardous Agents (Haz-Map)</p> | <p>This is an occupational health database designed for health and safety professionals and for consumers seeking information about the health effects of exposure to chemicals and biologicals at work.</p> <p>http://hazmap.nlm.nih.gov/</p> |
| <p>Household Products Database</p> | <p>The database is designed to help answer the following typical questions:</p> <ul style="list-style-type: none"> • What are the chemical ingredients and their percentage in specific brands? • Which products contain specific chemical ingredients? • Who manufactures a specific brand? • How do I contact this manufacture? • What are the acute and chronic effects of chemical ingredients in a specific brand? • What other information is available about chemicals in the toxicology-related databases of the National Library of Medicine? <p>http://hpd.nlm.nih.gov/index.htm</p> |

How to assess information for reliability, relevance and accuracy

The most reliable evidence linking a chemical to a resulting effect is obtained from statistically controlled clinical studies or workplace evaluations on humans. When data from human studies are not available, then data from animal studies are relied upon to draw inference about the potential hazard to humans. There are of course, uncertainties associated with extrapolating results from animal subjects to humans.

Reliability addresses the quality of a test report or publication: its methodology, the way the experimental procedure and results are described, and the clarity and plausibility of findings. It is important to distinguish between reliable *methods* and reliable *information*.

The process of determining the *quality* of data from existing documentation takes into account the following three aspects, defined by Klimisch et al. (1997):

1. **Reliability** - evaluating the inherent quality of a test report or publication. This aspect relates to the methodology, which should be standardized - and the way the experimental procedure and results are described. Findings should be supported with evidence for their clarity and plausibility;
2. **Relevance** - the extent to which data and tests are appropriate for a particular hazard identification or risk characterization; and
3. **Adequacy** - the usefulness of data for hazard /risk assessment purposes. When there is more than one study, most weight should be attached to those that are most reliable and relevant.

Systematic approach to determining data quality

Klimisch et al defined a systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data that has been coupled with a scoring system⁷ for reliability. The system consists of 4 reliability categories to enable ranking and organization of the information:

- 1. Reliable without restrictions:** “studies or data generated according to generally valid and/or internationally accepted testing guidelines (preferably performed according to GLP) or in which the test parameters documented are based on a specific (national) testing guideline or in which all parameters described are closely related/comparable to a guideline method.”
- 2. Reliable with restrictions:** “studies or data (mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are described, that cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable.”
- 3. Not reliable:** “studies or data in which there were interferences between the measuring system and the test chemical or in which organisms / test systems were used which are not relevant in relation to the exposure (e.g., non-physiological pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for assessment and which is not convincing for an expert judgment.”
- 4. Not assignable:** “studies or data which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc.).”

Data generated with OECD Test Guidelines in compliance with OECD GLP, the highest international quality standard, are recognized as of the highest quality and accepted in most countries⁸. High quality test data for substances and mixtures of physical hazards can be produced in accordance with internationally recognized test guidelines⁹. High quality test data for substances and mixtures of health and environmental hazards is generated by following internationally recognized Test Guidelines under OECD Good Laboratory Practice (GLP). For example:

- OECD Test Guidelines¹⁰
[www.oecd.org/department/0,3355,
en_2649_34365_1_1_1_1_1,00.html](http://www.oecd.org/department/0,3355,en_2649_34365_1_1_1_1_1,00.html)
- International Standard Organization (ISO) Guidelines¹¹
www.iso.org/iso/home.htm
- International Conference of Harmonization (ICH) Guidelines¹²
www.ich.org/cache/compo/276-254-1.html
- ASTM International¹³
www.astm.org
- European Union¹⁴
<http://ecb.jrc.ec.europa.eu/>
- US Environmental Protection Agency¹⁵
www.epa.gov/oppt/
- MITI (Japan)¹⁶
www.meti.go.jp/english/information/data/TESTindex.html

SECTION ONE PREPARATION

STEP 3: ALLOCATE SUBSTANCES INTO TIERS

In Step 2 you were shown how to gather the following information:

- Standard parameters
- Hazard information
- Exposure information

In Step 3, you will be shown how to use this information in order to:

- **Identify if your chemical has intrinsic hazard.**

Table 3, page 28 provides the information you need in order to be able to answer this question. The answer will determine which path of the decision tree you follow in order to allocate your substances into Tiers (see figure 2, page 26).

- **Identify use, dissemination and exposure control of the chemical**

In the workplace, along the supply chain, or to consumers.
See Table 4, page 32 to help answer this question.

- **Allocate chemicals into Tiers**

In order to prioritize the order in which your chemicals will be assessed for risk. The Tier-allocation also defines the appropriate level of information needed to be able to undertake the risk assessment.

Before embarking on Step 3, we need to first understand the GPS Tier System.

The Tier System

The GPS Tier system is based on a hazard / exposure rating (see figure 2 page 26). Progressively higher toxicological and ecotoxicological data requirements, are needed, depending the chemicals hazard and exposure potential. Substances with high to medium hazard and / or exposure potential are allocated to Tiers 1 and 2 for priority assessment. Substances with low to very low hazard and / or exposure potential are allocated to Tiers 3 and 4 for low priority risk assessment.

REMINDER: The Tier categorization is an efficient way of deciding which chemicals should undergo risk assessment in priority - and to ensure the appropriate level of information – called the *Base Set* – is gathered in order to be able to conduct the risk assessment. The Tier system does *not* indicate the level of risk. The calculation of risk will be explained later in Section Two, Step 7 (see page 122).

Tier 1: These substances are High Priority for risk assessment (higher hazard and / or exposure potential). In certain cases, more information needs to be gathered to complete your risk assessment or adequate risk reduction measures need to be defined after you have conducted your risk assessment.

Tier 2: These substances are Medium Priority for risk assessment (medium hazard and / or exposure potential). In certain cases, more information needs to be gathered to complete your risk assessment or adequate risk reduction measures need to be defined after you have conducted your risk assessment.

Tier 3: These substances are of Low Priority and required only limited risk assessment due to their low combined hazard and exposure potential, where likely exposure would result in low level impact. Such substances require a limited amount of data.

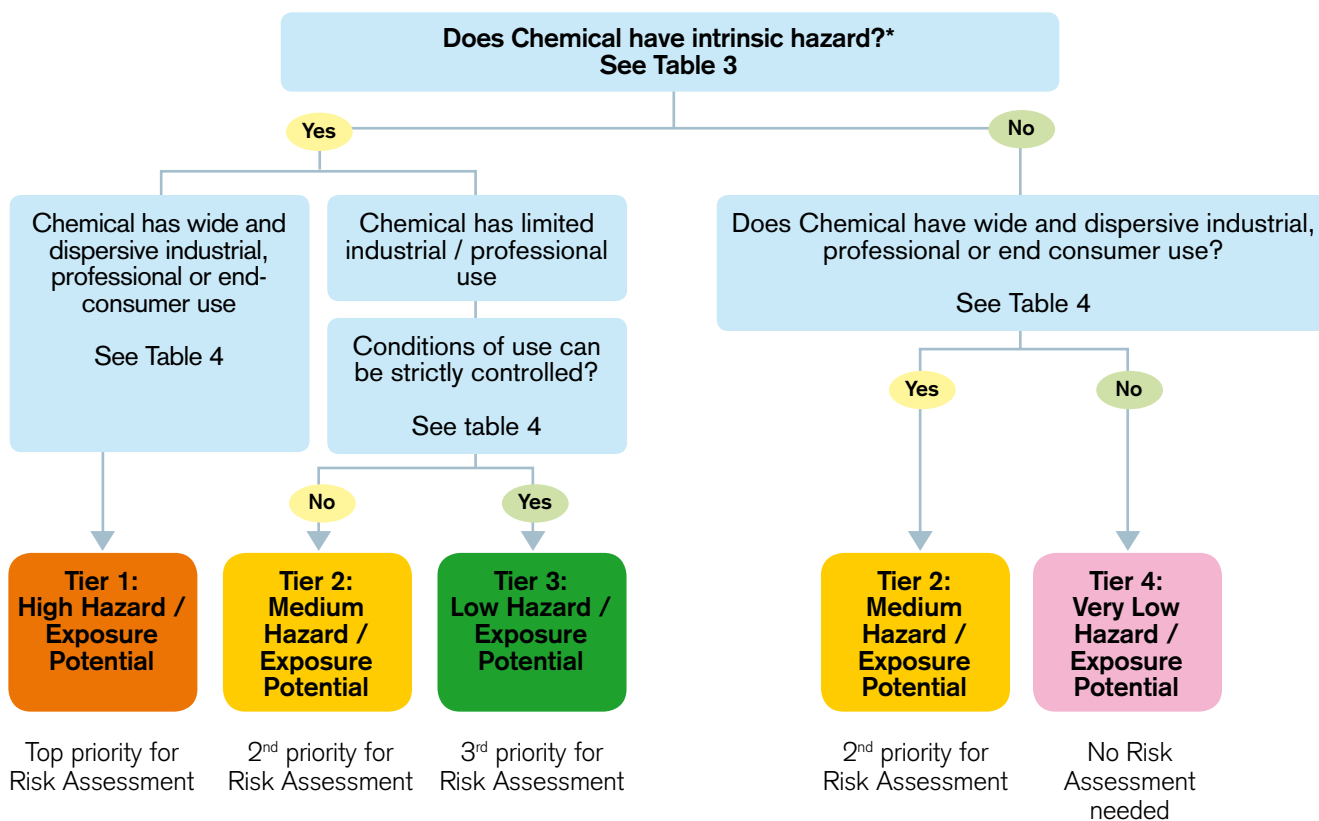
Tier 4: These substances are of Very Low Priority as they have no hazard potential. Examples include chemicals in REACH's list of non-dangerous substances, and those with minimal potential for exposure (non-isolated intermediate) where expected risks are minimal or non-existing. In most cases, Tier 4 substances require only the "Standard Parameters" gathered in Step 2 plus information on hazard potential for eye and skin irritation in case of accidental exposure.

SECTION ONE PREPARATION

STEP 3: ALLOCATE SUBSTANCES INTO TIERS

Allocating Substances into Risk Assessment Priority Tiers: Process

Figure 2: Decision Tree for allocating Substances into Tiers



* Check whether chemical is on Regulatory Candidate Lists. If yes, then follow legal requirements

Figure 2 summarizes the decision making process to follow in order to allocate substances into Tiers. Please refer to Figure 2 in conjunction with the text below, which describes the process in more detail.

Identify Intrinsic Hazard

Check your substance against the criteria in Table 3, page 28. Table 3 is consistent with the United Nations Globally Harmonized System (GHS) and uses basic information on hazard endpoint toxicity values in order to help the user identify the intrinsic hazard of the substance. Only reliable information on hazard endpoints should be used.

As you can see, Table 3 is color coded: At the first branch in the decision tree in Figure 2 if your substance lies within the **purple** columns, then you follow the **Yes** route of the decision tree. If your substance lies within the **blue** columns, then you follow the **No** route of the decision tree.

Identify use, dissemination and exposure control

Table 4 uses exposure categories expressed in the Use Descriptor terminology (page 92). As with the previous table, the color coding dictates which route you follow on the decision tree.

NOTE: In some cases, a chemical may be in a blue column for one endpoint and a purple column for another. In these circumstances, we advise taking the “worst case scenario” and allocating your chemical to the corresponding Tier in the purple column.

Allocate substances into Tiers

This enables prioritization of the chemicals for the next step: implementing the risk assessment process described in Section Two.

| Tier 1 = | Tier 2 = | Tier 3 = | Tier 4 = |
|--------------|--------------|---------------|---|
| Top priority | 2nd priority | 3rd priority. | lowest priority. Only further action required is to assess the acute toxicity potential of the chemical in case of accidental exposure (see page 58) |

If new information on hazard becomes available or the use and application of the chemical changes, the decision has to be revisited and - if indicated necessary - to be revised as appropriate.

Table 3: Assessing the intrinsic hazard of chemicals for the GPS Tier allocation system

a) Human health (based on GHS classification criteria)

| Hazard Endpoint | Decision | Decision | Decision | Decision |
|---|---|--|--|--|
| | Yes | Yes | No | No |
| Hazardous level | Level 1 | Level 2 | Level 3 | Level 4 |
| Acute Tox (skin / oral / inhalation) | Oral: LD50 ≤ 50 mg/kg, or dermal: LD50 ≤ 200 mg/kg, or inhalation (vapor): LC50 ≤ 2 mg/L, or GHS class 1 or 2 | Oral: 50 < LD50 ≤ 300 mg/kg, or dermal: 200 < LD50 ≤ 1000 mg/kg, or inhalation (vapor): 2 < LC50 ≤ 10 mg/L, or GHS class 3 | Oral: 300 < LD50 ≤ 2000 mg/kg, or dermal: 1000 < LD50 ≤ 2000 mg/kg, or inhalation (vapor): 10 < LC50 ≤ 20 mg/L, or GHS class 4 | Oral: LD50 > 2000 mg/kg, or dermal: LD50 > 2000 mg/kg, or inhalation (vapor): LC50 > 20 mg/L or GHS class 5 |
| Eye/Skin irritation | Corrosive Irreversible effects on the eyes GHS class 1 | Skin irritancy Eye irritancy GHS class 2 | Mildly irritating to the skin Mildly irritating to the eyes GHS class 3 | No irritancy |
| Sensitization | Respiratory sensitization (GHS class 1A) | Skin sensitization (GHS class 1A) Respiratory sensitization (GHS class 1B) | Skin sensitization (GHS class 1B) | No sensitization |

a) Human health (based on GHS classification criteria)

| Hazard Endpoint | Decision | Decision | Decision | Decision |
|---|--|---|--|---|
| | Yes | Yes | No | No |
| Hazardous level | Level 1 | Level 2 | Level 3 | Level 4 |
| Mutagenicity / Carcinogenicity | Probably carcinogenic or found positive for mutagenicity. Or GHS class 1A/1B | Possibly carcinogenic or mutagenicity suspected. Or GHS class 2 | Not likely to be carcinogenic in humans or mutagenic | Not carcinogenic in humans No mutagenicity |
| Repeated dose (skin / oral / inhalation) | NOEL ≤ 30 mg/kg/d, or GHS STOT class 1 | 30 < NOEL ≤ 300 mg/kg/d, or GHS class 2 | 300 < NOEL ≤ 1000 mg/kg/d | No effect found at the highest tested dose (1000 mg/kg/d) |
| Repro / Develop (skin / oral / inhalation) | NOEL ≤ 1 mg/kg/d, or GHS class 1A/1B | 1 < NOEL ≤ 100 mg/kg/d, or GHS class 2 | 100 < NOEL ≤ 1000 mg/kg/d | No effect found at the highest tested dose (1000 mg/kg/d) |

b) Environment (based on GHS classification criteria)

| Hazard Endpoint | Decision Yes | Decision Yes | Decision No | Decision No |
|-------------------------|--|---|---|--|
| Hazardous level | Level 1 | Level 2 | Level 3 | Level 4 |
| Acute toxicity | GHS Cat Acute 1 <1mg/l 96h LC50 (fish) 48h EC50 (daphnia) 72h/96h ER50 (algae) | GHS Cat Acute 2 >1<10mg/l 96h LC50 (fish) 48h EC50 (daphnia) 72h/96h ER50 (algae) | GHS Cat Acute 3 >1<10mg/l 96h LC50 (fish) 48h EC50 (daphnia) 72h/96h ER50 (algae) | No classification No acute toxicity |
| Chronic toxicity | GHS Cat Chronic 1 <1mg/l 96h LC50 (fish) 48h EC50 (crustacea) 72h/96h ER50 (algae) | GHS Cat Chronic 2 >1<10mg/l 96h LC50 (fish) 48h EC50 (crustacea) 72h/96h ER50 (algae) | GHS Cat Chronic 3 >1<10mg/l 96h LC50 (fish) 48h EC50 (crustacea) 72h/96h ER50 (algae) | No classification No chronic toxicity |
| Persistence | T1/2 marine, fresh water >60 d T1/2 marine, fresh sediment >180 d | T1/2 marine water >60 days, or fresh water >40 d T1/2 marine sediment >180 d, T1/2 soil >120 d | No data available | Not PBT |
| Bioaccumulation | BCF>5000l/kg | BCF>2000l/kg | No data available | Not PBT |

c) Phys.-chem. Hazards

| Hazard Endpoint | Decision Yes | Decision Yes | Decision No | Decision No |
|--------------------------------------|--|--|---|--------------------------------|
| Hazardous level | Level 1 | Level 2 | Level 3 | Level 4 |
| Flammability (GHS classification) | FP ≤ 23 °C AND Initial Boiling Point ≤ 35 °C | FP ≤ 23 °C AND Initial Boiling Point > 35°C | 23 °C < FP ≤ 60°C | 60°C < Flash Point (FP) ≤ 93°C |
| Reactivity | Readily detonates or explodes and decomposes under normal temperatures and pressures | Unstable Detonable Reactive with water | Unstable when heated or under pressure (not reactive with water) | No reactivity |

Table 4: Assessing the degree of dissemination / control of chemical substances

a) Worker / Consumer

| Type of Exposure | Decision | Decision | Decision | Decision |
|-------------------------------|---|--|---|--|
| Exposure level | Level 1 | Level 2 | Level 3 | Level 4 |
| Description | Consumer use; (assume exposure) Risk control: product design, instruction manuals | Professional use (eg. By craftsman); Risk control: personal protective equipment, organization-wide measures | Industrial use; Risk control: specialized facility/technology, organization-wide measures, personal protective equipment | Closed-system process |
| Examples in REACH PROC | PROC16 (Using material as fuel source, limited exposure to uncombusted product to be expected) PROC20 (Heat and pressure transfer fluids in dispersive use but closed-systems) | PROC8a (Transfer of substance or preparation from/to large containers at non-dedicated facilities) PROC10 (Roller application or brushing of adhesive and other coating) PROC11 (Spraying outside industrial settings or applications) | PROC4 (Use in batch and other process [synthesis] where opportunity for exposure arises) PROC5 (Mixing or blending in batch processes for formulation of preparations and articles [multistage and/or significant contact]) PROC6 (Calendering operations) PROC7 (Spraying in industrial settings and applications) PROC9 (Transfer of substance or preparation into small containers [dedicated filling line, including weighing]) | PROC1 (Use in closed-system process, no likelihood of exposure) PROC2 (Use in closed-system, continuous process with occasional controlled exposure [e.g. sampling]) PROC3 (Use in closed-system batch process [synthesis or formulation]) |

b) Environment

| Type of Exposure | Decision | Decision | Decision | Decision |
|---------------------------------|--|--|--|--|
| Exposure level | Level 1 | Level 2 | Level 3 | Level 4 |
| Description | Professional/Consumer use (Emission of substances: Intentional) e.g. products for personal care, cleaning, agrochemical use | Professional/Consumer use (Emission of substances: Not intended) e.g. adhesives, coating agents | Industrial operations - Emission control: technical (end of pipe) organization-wide measures | Industrial operations - Emission control: closed/strictly-controlled system |
| Examples in REACH (ERC)* | <p>ERC8a (Wide dispersive indoor use of processing aids in open-systems)</p> <p>ERC8b (Wide dispersive indoor use of reactive substances in open-systems)</p> <p>ERC8d (Wide dispersive outdoor use of processing aids in open-systems)</p> <p>ERC8e (Wide dispersive outdoor use of reactive substances in open-systems)</p> <p>ERC10b (Wide dispersive outdoor use of substances included into or onto articles and materials that have a long service life and from which the release of the substances is intended or high)</p> <p>ERC11b (Wide dispersive indoor use of substances included into or onto articles and materials that have a long service life and from which the release of the substances is intended or high)</p> | <p>ERC8c (Wide dispersive indoor use of substances which will be bound into or onto a matrix or material)</p> <p>ERC8f (Wide dispersive outdoor use of substances which will be bound into or onto a matrix or material)</p> <p>ERC9a (Wide dispersive indoor use of reactive substances in open-systems)</p> <p>ERC9b (Wide dispersive outdoor use of reactive substances in open-systems)</p> <p>ERC10a (Wide dispersive outdoor use of substances included into or onto articles and materials that have a long service life with low-release)</p> <p>ERC11a (Wide dispersive indoor use of substances included into or onto articles and materials that have a long service life with low-release)</p> | <p>ERC2 (Formulation of preparations)</p> <p>ERC3 (Formulation in materials)</p> <p>ERC4 (Used as processing aids in production or processes and not made into finished products)</p> <p>ERC5 (Use of substances that are bound into or onto a matrix or material)</p> | <p>ERC1 (Production of chemicals)</p> <p>ERC6a (Use of intermediates)</p> <p>ERC6 (Use of reactive processing aids)</p> <p>ERC6c (Use of monomers in the production of polymers)</p> <p>ERC6d (Use of processing aids in the production of polymers and rubbers)</p> <p>ERC7 (Use of substances in closed-systems)</p> |

SECTION ONE PREPARATION

STEP 4: DEVELOP TIER-RELEVANT INFORMATION (“BASE SET TIER”)

In Step 4 you will be shown how to:

- **Identify exemptions:** chemicals that possess certain properties (e.g. phys-chem.) that exempt them from certain information requirements of the Tier system
- **Gather Tier-relevant information:** in order to conduct a risk assessment on each chemical according to its Tier allocation
- **Identify and fill information-gaps** by resourcing information from alternative sources, for example extrapolation or generation of new data

PLEASE NOTE: Before embarking on Step 4, we must first understand the following:

- (1) A key aspect of the Tier system is that it defines the degree of information (the “Base Set”) required to assess the risk of each substance: an important cost / time-saving step. The level and amount of information depends on the priority for assessment defined by the chemicals hazard / exposure rating, and expressed by its Tier-allocation. Not all chemicals have the same information requirement: chemicals that are more hazardous or widely disseminated require more toxicological and ecotoxicological data for the risk assessment than less hazardous substances or those that are well controlled.
- (2) In this way, Tier 1 substances have the highest Base Set information requirement whilst Tier 4 substances have the lowest. In general, Tier 4 substances only require the level of information already gathered in Step 2 plus additional minimal information in case of accidental exposure, see page 38. On the other hand, more information – over and above that explained in this guidance document may be required for Tier 1 substances.
- (3) The GPS Base Set of information is specific for each Tier allocation. It is the starting point: the minimum information required to assess the risk of most chemicals in commerce. However, in cases of significant hazard or exposure potential (for example highly toxic chemicals or carcinogens) additional data generation may be justified. In these situations (to be identified case-by-case), the Base Set might need to be extended: see the “GPS Guidance Manual on Triggers”. Alternatively, the data should be increased to fit the requirements of the next higher Tier.

The Base Set Tier

In order to conduct robust risk assessment and risk management, GPS recommends developing a Base Set of Information for each chemical sold in the market or transported from the production site. The Base Set of information is dependent upon the Tier allocation of the chemical. Once complete, we call the information gathered the “**Base Set Tier**”.

Base Set Tier = Standard Parameters (Step 2) + Tier-specific information (Step 4)

Identify Exemptions

In specific cases, information on some end points cannot be obtained. Box 5 gives some examples. All deviations must be properly justified and documented based upon a weight of evidence approach or a quantitative exposure assessment.

Box 5: Exceptions to fulfilling the Tier-specific information elements

- For chemicals which have an obviously high boiling point and low vapor pressure (e.g. some inorganic or organic salts), an estimation of these two phys-chem. endpoints could be sufficient.
- Testing is technically not feasible: Testing for a specific endpoint may be omitted if it is technically not possible to conduct the study as a consequence of the properties of the chemical. Testing may be omitted based on physico-chemical properties of a chemical, such as low water solubility, vapor pressure, reactivity, that preclude the application of certain test methods. Administration of precise and consistent doses of a chemical may be impossible because of its physico-chemical properties e.g. testing of non-water soluble compounds for fish toxicity in submerged cell cultures. For further information see OECD Series on testing and assessment Nr. 23, Guidance document on aquatic toxicity testing of difficult chemicals and mixtures
- Endpoint information for one chemical is used to make a prediction of the endpoint for another chemical (read across) which is considered to be “similar” (see page 36)

SECTION ONE PREPARATION

STEP 4: DEVELOP TIER-RELEVANT INFORMATION (“BASE SET TIER”)

Gather Tier-relevant information

Table 5 below summarizes the hazard parameters or “endpoints” for which hazard information must be gathered based on the Tier allocation of the chemical.

NOTE: For certain substances, additional information based on their high hazard potential – over and above that outlined in this document – might be required. In this case refer to the new GPS Guidance Manual on Triggers (currently under development) for on advice on additional information requirements for these chemicals.

Table 5: Hazard “end points” for which information must be gathered according to Tiers

a) Human health

| Tier 1 (High hazard and/or high exposure potential) | Tier 2 (Medium hazard and/or medium exposure potential) | Tier 3 (Low hazard and/or low exposure potential) | Tier 4 (Very low hazard and/or very low exposure potential) |
|---|---|---|---|
| Irritation (Eye / Skin) | Irritation (Eye / Skin) | Irritation (Eye / Skin) | Irritation (Eye / Skin) in case of accidental exposure |
| Mutagenicity (e.g. Ames, mammalian cell in vitro, in vivo micronucleus) | Mutagenicity (e.g. Ames, mammalian cell in vitro, in vivo micronucleus) | Mutagenicity (e.g. Ames test) | |
| Sensitization | Sensitization | Sensitization | |
| Repeated dose toxicity | Repeated dose toxicity | | |
| Reproduction / developmental toxicity test | | | |

b) Environment

| Tier 1 (High hazard and/or high exposure potential) | Tier 2 (Medium hazard and/or medium exposure potential) | Tier 3 (Low hazard and/or low exposure potential) | Tier 4 (Very low hazard and/or very low exposure potential) |
|--|---|---|---|
| Acute Toxicity to Fish | Acute Toxicity to Fish | In case of accidental exposure relevant ecotoxicological data is needed | Acute Toxicity |
| Acute Toxicity to Daphnia | Acute Toxicity to Daphnia | | |
| Acute Toxicity to Algae | Acute Toxicity to Algae | | |
| Chronic Toxicity (fish or daphnia) within limitations of the chemical properties | | | |

SECTION ONE PREPARATION

STEP 4: DEVELOP TIER-RELEVANT INFORMATION (“BASE SET TIER”)

Identify and fill information-gaps

The information sources identified in Step 2 should provide you with most of the information you require. However, should this be insufficient, you will need to:

1. Extrapolate data from other sources, or
2. Generate new data. This option is the last resort in order to minimize animal testing.

1. Extrapolate data from other sources

- **Data-sharing between companies**

Companies can use systems related to regulations of chemicals such as REACH-IT for data-sharing. To promote data-sharing, ICCA is developing a GPS IT Portal that will provide its members with access to hazard information owned by companies.

- **Route-to-route extrapolation and extrapolation between exposed populations using historical data such as publicly available epidemiological studies** even when the exposure routes and exposed populations of existing data do not match the endpoints, they may still be useful: e.g. oral sub-chronic toxicity data can be used to assess long-term risk of consumer dermal exposure. Here, extrapolation and correction of data based on differences in routes and species is needed.

- **Read-across and estimation from related substances¹⁷**: Endpoint information for one chemical is used to make an endpoint prediction for another chemical, considered “similar” (e.g. OECD HPV program¹⁸). This complex approach should only be performed by an experienced scientific expert. If no data is available on the target substance, then an assessment may be undertaken using data on related substances. Data from structurally similar chemicals can be leveraged (referred to as “category approach, read across”). Chemicals sharing key features can be allocated into chemical categories: groups of chemicals whose physico-chemical; human health, ecotoxicological and environmental fate properties are likely to be the same or follow a regular pattern. The final data set must enable assessment of the untested endpoints, ideally by interpolation between category members. Similarities include:

- Common functional groups (e.g. aldehyde, epoxide, ester, specific metal ion);
- Common constituents or chemical classes, similar carbon range numbers
- Incremental and constant change across the category (e.g. chain-length category)
- Likelihood of common precursors and/or breakdown products, via physical or biological processes, which result in structurally similar chemicals (e.g. the metabolic pathway approach of examining related chemicals such as acid / ester / salt).

2. Generate New Data

Increasing awareness of animal welfare has emphasised the need to reduce use of laboratory animals. Alternative tests with cultured cells (in vitro models) or computer modelling (QSAR) should be favoured whenever feasible, reliable and appropriate. For more information on which method can be used for which toxicological endpoint please refer to page 56).

- ***In vitro* methods**
Non-animal testing data generated using methods validated in accordance with internationally accepted principles (e.g. ECVAM, OECD)
- **(Quantitative) Structure Activity Relationships / Computer Modeling (QSAR)**
Theoretical models used to predict the physicochemical and toxicological properties of molecules based on the chemical structure (applicable if structure is in domain). However, only validated models should be used and it has to be evaluated upfront whether the model is appropriate for the respective chemical class (e.g. HPV and REACH offer examples where the category approach has been accepted).

REACH guidance on QSAR prediction models¹⁹ can be found on:
http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r6_en.pdf?vers=20_08_08

ECB guidance on QSAR models and their validity²⁰ can be found on:
www.oecd.org/dataoecd/33/41/37850114.pdf

SECTION ONE PREPARATION

STEP 4: DEVELOP TIER-RELEVANT INFORMATION (“BASE SET TIER”)

Animal tests should always be the “last resort”, reserved until all the existing data have been evaluated. Tests should adopt standardized methods included in guidelines such as the OECD Test Guideline, and need to be conducted in compliance with GLP. High quality test data for health and environmental hazards can be generated by following internationally recognized Test Guidelines under OECD Good Laboratory Practice (GLP)²¹.

Box 6: Additional internationally recognised Test Guidelines

- OECD Guidelines for the Testing of Chemicals
http://www.oecd.org/document/40/0,3343,en_2649_34377_37051368_1_1_1_1,00.html
- International Conference of Harmonization (ICH) Guidelines
www.ich.org/cache/compo/276-254-1.html
- ASTM International
www.astm.org
- European Union, Council Regulation (EC) No 440/2008
http://eurlex.europa.eu/Result.do?T1=V2&T2=2008&T3=440&RechType=RECH_naturel&Submit=Search
- MITI (Japan)
www.meti.go.jp/english/information/data/TESTindex.html

SECTION TWO IMPLEMENTATION

By following the four steps in Section One, you prepared the ground for the implementation of the GPS risk assessment. Upon completion of Section One, you have:

- Gathered the information required to implement the GPS risk assessment system
- Categorized your chemicals according to their priority for risk assessment (the Tier allocation)
- Developed further information, according to the Tier-categorization

In Section Two, you will take the results of Section One: analyze them and put them in perspective by implementing the four individual steps below. Section Two is the implementation phase of the GPS risk assessment process.

Box 7: The 4 Steps of the GPS Risk Assessment “Implementation” Section

STEP 5: Characterize the hazard in order to determine whether the chemical has the potential to cause adverse effects for human health and / or the environment

STEP 6: Assess the likely real-life exposure situations: the exposure assessment

STEP 7: Compare the level that could cause an adverse effect with the estimated exposure and characterize the magnitude of potential risk from the substance. Identify if needed risk management measures to minimize risks.

STEP 8: Document results and communicate relevant outcomes to the public in the format a GPS Safety Summary.

Hazard Characterization

A chemical's potential to cause toxic or adverse effects is known as intrinsic hazard. Hazard Characterization is the process of determining if exposure to a chemical can cause adverse effects (e.g., cancer, birth defects, sensitization, etc.). Because some hazard effects are limited to the tested animal species, hazard characterization also determines whether the adverse effect is likely to occur in humans.

Some chemicals have the potential to cause harmful effects – referred to as toxic or adverse effects in this guidance document. An adverse effect is defined as an abnormal, undesirable or harmful change following exposure to a potentially toxic chemical.

In Section One, you gathered all available information on the chemical(s) and their potential hazards. However, a chemical's intrinsic hazard will only manifest as an adverse effect if and when a set of conditions are met (a certain level of exposure, threshold of effect, incorrect handling and use). Therefore, in Step 5 you will evaluate and integrate the information gathered in so far – in order to derive hazard threshold levels for the following human health and environmental endpoints (see Supplement, page 56 for more information on the hazard endpoints):

Box 8: Overview of GPS Hazard endpoints for Human Health and the Environment

| Human Health End Points | Environmental End Points |
|--|---|
| <ol style="list-style-type: none">1. Acute toxicity2. Irritation and Corrosivity3. Sensitization4. Mutagenicity and Genotoxicity5. Repeated Dose toxicity6. Reproductive / Developmental toxicity | <ol style="list-style-type: none">1. Aquatic toxicity2. Degradation, bioaccumulation |

Prior to embarking on Step 5, it is important to take into account the considerations below. The Supplement starting on page 56 gives more detail should you need it.

SECTION TWO IMPLEMENTATION

STEP 5: CHARACTERIZE HAZARD

General considerations when analyzing hazard data

- 1. The endpoints in the hazard assessment are interrelated:** Information collected for one endpoint may influence hazard/risk assessment of another endpoint - and may be used for more than one endpoint.
- 2. Degradation products and metabolites should be considered:** The products of degradation and metabolism of the substance may need further investigation if relevant for the risk assessment; PBT (persistent, bioaccumulating and toxic) assessment or classification and labelling
- 3. The appropriate route of exposure for toxicity testing should be selected:** Exposure occurs when a chemical comes into contact with the organism (e.g. human). The route of exposure is the pathway by which a chemical enters the body: penetration through the skin (dermal absorption), absorption through the lungs (inhalation) or the digestive tract after ingestion (oral). Most chemicals are not equally toxic by all three exposure routes. Usually, experiments use the route through which humans are most likely to be exposed, but other more convenient routes can be chosen for many tests. To identify the most appropriate exposure route, all available information on human exposure should be considered. Route-to-route extrapolation may be possible on a case-by-case basis.
- 4. Test System Sensitivity:** The observed threshold dose/effect level in a toxicity test depends upon the sensitivity of the test system.
- 5. Dose-response:** "Dose" indicates the concentration of the chemical administered while "response" refers to its effect. The assessment of dose-response relationships is complex: a single dose-response relationship cannot model all adverse effects and all populations. Toxicity depends on the amount of a chemical absorbed into the body as well as the pathway that the chemical follows once it has entered the circulation. Adverse health effects are only expressed when the chemical, or its active metabolite, reaches a threshold concentration in the relevant organ. This in turn depends upon both the level of exposure and the route of exposure, and the level of elimination from and degradation in the targeted organ: the threshold exposure concentration may vary considerably for different exposure routes and for different species, because of differences in toxicokinetics and mechanisms of action. To quantitatively assess the effects of a chemical substance, the relationship between the amount of exposure and its health effects (dose-dependency evaluation) must be understood (see page 80).

6. Identification of critical data (key studies): For a particular endpoint, data from more than one study might be available (e.g. in different species, with different durations). Therefore it is important to identify key studies (critical data) for each hazard. Critical data represent the best quality / reliable data within the hazard data under evaluation (See page 120).

7. Dose Descriptors: As part of the evaluation of toxicity studies, dose descriptors (e.g., NOAEL, NOEL, NOAEC, BMD, LD50, LC50, and T25) should be identified for the endpoint concerned. More than one dose descriptor for the endpoint may be identified. These are used as starting point values (point of departure) to calculate and correct reference values that indicate the permissible exposure level (for more information see page 79).

The Hazard Characterization Process

Two main approaches to hazard characterization and subsequent risk assessment exist. Both follow the same basic methodology in that they use Dose Descriptors and Assessment (uncertainty) factors, and ultimately lead to the same conclusion. However, the way the outcome is presented is different:

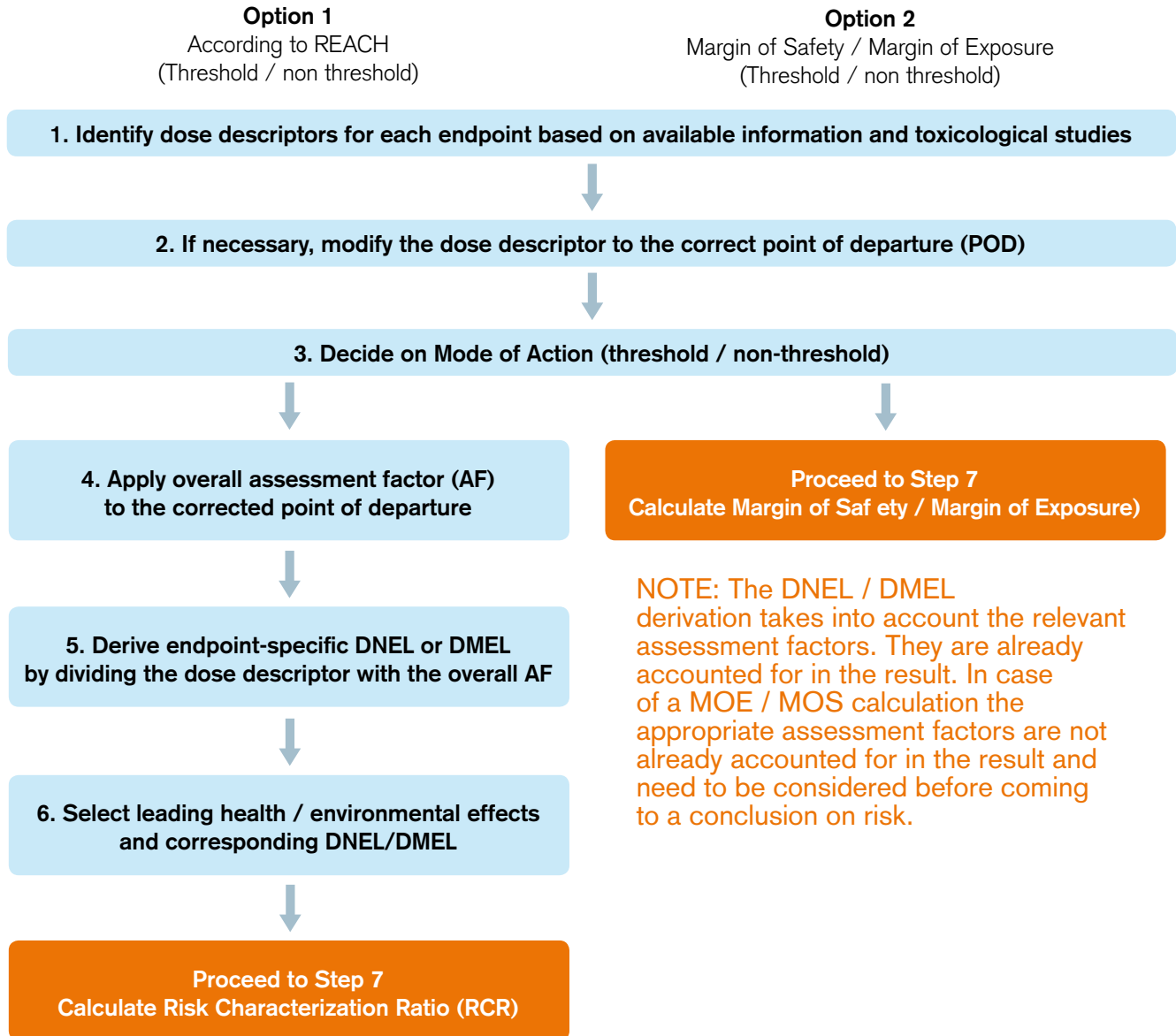
1. MOS/MOE: The classical approach is the derivation of a Margin of Safety (MOS), also termed Margin of Exposure (MOE). Here, assessment factors are considered after deriving the result. If new exposure information becomes available, the MOS/MOE conclusion may need to be re-calculated.

2. DNEL: In Europe, REACH legislation has established the Derived No Effect Level (DNEL). The advantage of this approach is that it is directly comparable to exposure estimates and measurements, so if new exposures become available, they are easily compared with the existing DNEL. Also, assessment factors are accounted for in the process of the DNEL derivation and therefore are included in the result. See page 83 for a worked through DNEL calculation.

SECTION TWO IMPLEMENTATION

STEP 5: CHARACTERIZE HAZARD

Figure 3: Hazard characterization process: DNEL and MOE/MOS



The guidance below describes each stage in the hazard characterization process: first for human health and then for the environment. Please read it in conjunction with Figure 3 above. The first three stages are identical for both the MOE/MOS and the DNEL approach. DNEL then has an additional three stages before both DNEL and MOE/MOS end in the Risk Characterization Step – described in Step 7, page 115.

Characterizing Human Health Hazards (MOS/MOE and DNEL)

1. Identify dose descriptors for each endpoint based on available information and toxicological studies

Using the information gathered in Section One, identify dose descriptors for each relevant hazard endpoint (e.g. NOAEL, NOAEC, BMD, LD50, LC50, T25). See page 79 for more information on dose descriptors and page 56 for guidance on health hazard endpoints.

Most adverse health effects are expressed only if the substance or its active metabolite reaches threshold dose in the relevant tissue or organ. Below threshold dose, no effect will occur. The threshold dose is derived by analyzing animal study results and formulating the “no observed adverse effect level” (NOAEL), or the “lowest observed adverse effect level” (LOAEL). NOAELs are derived from effects seen in sub-acute, sub-chronic, chronic and reproductive toxicity tests – they cannot be derived from acute toxicity, irritation or skin sensitization tests because of their study design.

The NOAEL is the highest dose or concentration of the substance used in that particular test, at which no statistically significant adverse effects were observed. For example if the dose levels of 400, 100, 50 and 5 mg.kg⁻¹.day⁻¹ of a substance have been used in a test, and adverse effects were observed at 400, 100 and 50 mg.kg⁻¹.day⁻¹ but not at 5 mg.kg⁻¹.day⁻¹, the derived NOAEL will be 5 mg.kg⁻¹.day⁻¹.

SECTION TWO IMPLEMENTATION

STEP 5: CHARACTERIZE HAZARD

Situations where no dose descriptors are available: Hazard characterization for a particular endpoint depends on the availability of at least one study identifying an adverse effect – enabling the determination of a NOAEL/LOAEL. If no effects are seen at the highest dose level, then no NOAEL or LOAEL can be derived. In these cases, GPS recommends the following:

- Assess if the chemical is likely to demonstrate significant toxicity towards the particular endpoint. This requires expert judgment and considers knowledge of the endpoint, the chemical's database – including possible (Q)SAR evidence, and the dose levels tested.
- If the dose levels tested are sufficiently high, and it is judged that the chemical is unlikely to possess significant toxicity towards that endpoint – *then* it can be concluded that there is no risk for that particular endpoint. If not, then:
- Conduct a DNEL or the MOS/MOE calculation described in Step 7 (see page 115) using the highest dose tested as the NOAEL. *If* the calculated MOS/MOE is considered sufficiently high, then the conclusion is clear: no concern. However, *if* the MOS/MOE is small then the exposure scenarios are likely to show significant human exposures.
- The final option is to ask for more data – taking animal welfare issues and conclusions from other endpoints into account.

2. If necessary, modify the dose descriptor to the correct point of departure (POD)

In certain situations, the dose descriptor may not be directly comparable to the exposure assessment. This can occur for a variety of reasons, for example interspecies differences in bioavailability between experimental animals and humans; the animal dose descriptor might relate to a different exposure route than the human exposure - requiring route-to-route extrapolation; differences in human and experimental exposure time conditions or differences in respiratory volumes between experimental animals and humans.

In these situations, it is necessary to modify the dose descriptor (e.g. NOAEL) for the threshold effect into an appropriate starting point: the Point of Departure (POD) for the threshold effect. A POD marks the beginning of extrapolation to lower doses. It is an estimated dose (usually expressed in human-equivalent terms) near the lower end of the observed range, without significant extrapolation to lower doses.

NOTE: In the absence of information, the default is to assume the same bioavailability for experimental animals and humans for a particular exposure route.

3. Decide on Mode of Action (threshold / non threshold)

Certain chemicals are thought to impose a carcinogenic risk without a threshold. The relevant carcinogenic mechanism is thought to operate even at the smallest exposure concentration. For these chemicals the conventional NOAEL and safety factor approach to derive exposure standards is not appropriate. Within REACH the process to arrive at exposure standards for these theoretically non-threshold carcinogens is described in the DMEL (derived minimal exposure level) process. The DMEL expresses an exposure level corresponding to a certain risk number, that appears to be tolerable though it is higher than zero. DMEL derived in accordance with the guidance is considered to be a tolerable level of effects. However, it must be stressed that for carcinogens and mutagens workplace exposures should be avoided / minimized as far as technically feasible. There are default methodologies which can be applied for deriving a DMEL. One is based on linear extrapolation from animal bioassay data and the other is a threshold approach based on application of uncertainty factor (UF) to a suitable reference point on the dose-response for carcinogenicity.

4. Apply overall Assessment Factor (AF) to the corrected point of departure

Uncertainties in the extrapolation of experimental animal test data to real human exposures are addressed by applying Assessment Factors (AF). For example, individual AF's address the difference in exposure duration between the experimental data and the assumed real-life exposure for humans; the route of exposure if different for humans; differences in sensitivity of response between species (inter-species) and within species (intra-species). The individual assessment factors for each uncertainty identified are applied to the corrected dose descriptor in order to arrive with an overall AF for that particular dose descriptor.

Expert judgement on the part of the risk assessor is required to weigh these individual parameters on a case-by-case basis. After identifying the relevant individual assessment factors, the overall assessment factor is obtained by simple multiplication of the individual AFs.

NOTE: Different guidance documents sometimes use different terminology for the factors applied: It is generally understood that *Adjustment Factors* are numerical values that adjust dose to ensure normalisation for species or duration, while *Uncertainty Factors* are numerical values that are used to account for lack or poor quality of information. The term *Assessment Factor* is used for a numerical value, which covers both dose adjustment and data uncertainty.

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Assessment factors account for the following situations

- **Time extrapolation:** A sub-acute or sub-chronic study in rodents is often used for extrapolation to a lifetime NOAEL (reflecting a *chronic* exposure). Sub-acute usually refers to a 28 day study, *sub-chronic* to a 90 day study, and chronic to a 1.5-2 year study, the latter being the lifespan for rodents.
- **Route-to-route extrapolation:** Route-to-route extrapolation is only feasible for substances with a systemic mode of action. It is not appropriate for substances with a local mode of action (e.g. corrosive substances) where tissue damage is more dependent on concentration and local tissue deposition, than on dose. Route determines the rate of absorption, distribution, metabolism and excretion of the chemical. ECHA proposes that: "in the absence of specific information on the starting route, a default factor of 2 is included (i.e. the absorption percentage for the starting route is half that of the end route) in the case of oral-to-inhalation extrapolation. The inclusion of this factor of 2 means that 50% (instead of 100%) absorption is assumed for oral absorption, and 100% for inhalation. Note that if data on the starting route (oral) are available these should be used, but for the end route (inhalation), the worst case inhalation absorption should still be assumed (i.e. 100%). Note that this does not apply if there is a first pass effect, if there is non-resorption, or for bolus effects."²²
- **Interspecies differences:** the default assumption is that humans are more sensitive than the experimental animal. In their May 2008 guidance, ECHA provides allometric scaling factors for different species as compared to humans:
- **Intra-species extrapolation:** Humans differ in sensitivity to toxic insult due biological factors such as genetic polymorphism affecting toxicokinetics/metabolism, age, gender, health status and nutritional status. These differences can be the result of genetic or environmental influences. Intra-species variation is greater in humans than in the more inbred experimental animal population. For threshold effects, a factor of 10 is the standard default procedure when assessing exposure to the general population. It is recognized that there are differences between children and adults in toxicokinetics (especially babies in their first months) and toxicodynamics (especially at different stages of development). These differences may render children more or less susceptible to the toxic effects of a substance. A higher intra-species assessment factor for children should be considered in certain cases.

For more information on AF, refer to the ECETOC Technical Report No. 86. ECHA provides default AFs for specific situations²³ (see page 82).

5. Derive endpoint-specific DNEL or DMEL by dividing the dose descriptor by the overall AF

There are default methodologies which can be applied for deriving a DMEL. One is based on linear extrapolation from animal bioassay data and the other is a threshold approach based on application of uncertainty factor (UF) to a suitable reference point on the dose-response for carcinogenicity. For a worked through DMEL derivation example refer to page 86.

- (i) *Linear extrapolation from animal bioassay data (quantitative approach)*: The DMEL is derived by linear extrapolation from the tolerable lifetime cancer risk (e.g. of 10^{-4} , 10^{-5} and 10^{-6}) calculated from a defined POD close to the experimental dose range (e.g. a T25 or a BMD10 cancer incidence in a rodent long-term cancer bioassay).
- (ii) *Threshold Approach*: The threshold of toxicological concern (TTC) is a principle which refers to the possibility of establishing a human exposure threshold value, below which there is no appreciable risk to human health (by the oral route) generated in the past. Currently, the TTC concept is used for regulatory purposes in the risk assessment of flavorings and food additive substances. A more extended description of the TTC concept is presented in the ECHA Guidance Appendix R.7-1.

In order to derive endpoint-specific DNEL(s) for the relevant exposure pattern (duration, frequency, route and exposed human population), the overall AF is to be applied directly to the corrected dose descriptor(s) in the following manner (in this example, NOAEL or NOAEC are used as the dose descriptor).

Data from more than one valid and relevant study may be available (e.g. in different species, with different durations), identifying more than one dose descriptor to a given endpoint. Since it is not possible to know beforehand which of these dose descriptors will turn out to be the most relevant for the endpoint-specific DNEL, it might be necessary to derive DNELs for more than one dose descriptor per endpoint, prior to selecting the lowest DNEL for that endpoint. This will be a case to case decision and depend on expert judgment.

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$$\text{DNEL} = \frac{\text{NOAEL or NOAEC}}{\text{AF1} \times \text{AF2} \times \dots \times \text{AFn}} = \frac{\text{NOAEL or NOAEC}}{\text{Overall Assessment Factor}}$$

If Exposure < DNEL → Risk is adequately controlled

If Exposure > DNEL → Risk is NOT adequately controlled

NOTE: Justification must be given for the choice of the information used, the route of exposure (oral, dermal, inhalation) and the duration and frequency of exposure to the substance for which the DNEL is valid.

Situations where no DNEL can be derived: Certain chemicals are considered to impose a carcinogenic risk without a threshold and their carcinogenic mechanism is of concern at the smallest exposure concentration. For these chemicals the conventional NOAEL and safety factor approach to derive exposure standards is not appropriate. In these circumstances two options are available: (i) the calculation of a DMEL (derived minimal exposure level), as described in the European REACH legislation; or (ii) the calculation of the MOE (margin of exposure), as described by the European Food Safety Agency for situations where no threshold can be calculated.

- **DMEL:** Within REACH the process to arrive at exposure standards for these theoretically non threshold carcinogens is described in the DMEL (derived minimal exposure level) process. The DMEL expresses an exposure level corresponding to a certain risk number, that appears to be tolerable though it is higher than zero. DMEL derived in accordance with the guidance is considered to be a tolerable level of effects. However, it must be stressed that for carcinogens and mutagens workplace exposures should be avoided / minimized as far as technically feasible.
- **MOE:** An alternative quantitative approach is the assessment of the Margin-of-Exposure (MOE) which is recommended by EFSA (European Food safety Agency) in assessing risks associated with substances which are both genotoxic and carcinogenic. The MOE is the ratio between human exposure and a defined, experimental cancer incidence (e.g. the T25 or BMD10 value in a rodent long-term cancer bioassay, or reliable human cancer data from epidemiological studies). The ratio between exposure (e.g. in the workplace) and the T25/ BMD10 values should be several orders of magnitude. Alternatively, the T25 or BMD10 cancer potency values could be divided by a special assessment factor for high-to-low-dose extrapolation which may be applied in addition to conventional assessment factors for e.g. inter- and intra-species variation. The accepted risk levels (e.g. of 10^{-4} , 10^{-5} and 10^{-6}), appropriate magnitudes of MOE/MOS as well as the magnitude of the additional high-to-low-dose extrapolation assessment factor would have to be harmonized and accepted at the policy level. For more information see page 118.

6. Select leading health effects and identify corresponding DNEL/DMEL

After deriving your endpoint-specific DNEL or DMEL, select the leading health effect(s) and the corresponding DNEL/DMEL. These critical DN/MELs should be the lowest DN/MEL obtained for each exposure pattern. They will be used to characterize risk in Step 7 (see page 114).

Characterising Environmental Hazards

1. Identify dose descriptors for each endpoint based on available information and toxicological studies

Environmental hazard characterisation is conducted in a similar manner as for human health. Here PNECs (predicted no effect concentration) are used as dose descriptors and derived from the data collected in Section One. PNECs usually result from single species laboratory toxicity tests (e.g. fish, algae, and daphnia). Data are typically reported as the concentrations at which x% (e.g. 50%) mortality or inhibition of function (e.g. growth) is observed. PNECs are expressed as the lethal concentration (LCx) or the effect concentration (ECx), e.g. LC50 or EC50.

The endpoints most frequently used for derivation of PNEC are mortality (LC50), growth (ECx or NOEC) and reproduction (ECx or NOEC). A PNEC must be calculated for each environmental compartment in which exposure is expected (air, water, sediment and soil).

Under normal circumstances, qualitative assessments are valid for atmospheric (air) exposure only. For the hydrospheric (water) compartment, PNECs should be calculated from long-term toxicity studies using NOECs (no observed effect concentrations). Sometimes, water is the only environmental compartment for which toxicity studies can be conducted. In such cases, PNECs for the sediment and soil compartments can be estimated by equilibrium partitioning of data from aquatic organisms²⁴. If data from long-term toxicity studies are not available, then the PNEC can be derived from short-term (acute) toxicity data (LC50 or EC50). Here, a larger assessment factor is required.

$$\text{PNEC} = \text{L(E)C50} / \text{AFs}$$

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2. Apply overall assessment factor (AF) to the corrected point of departure

The purpose of assessment factors is to allow extrapolation from laboratory toxicity test data to ecosystem effects. To calculate a PNEC from the available data, the experimentally determined no observed effect concentration (NOEC) is divided by an assessment factor, selected according to the strength of the available data:

Table 6: Calculation of assessment factor according to available data

| Data available | Default assessment factor |
|--|---------------------------|
| Acute toxicity data from more than one species (applied to the lowest L(E)C50) in place of NOEC) | 1000 |
| Chronic toxicity data where data are 50 not necessarily from the most sensitive species (applied to the species lowest NOEC) | 50 |
| Chronic toxicity data based on 10 data from the most sensitive species (applied to the lowest NOEC) | 10 |

An assessment factor of 10 is normally only be applied when chronic toxicity NOECs are available from three species across three taxonomic groups (e.g. fish, Daphnia, and algae). If there is evidence that the most sensitive species has been tested, the factor may be applied to the lowest value from two species. When examining the results of chronic data, the PNEC should, where possible, be calculated from the lowest available NOEC. Extrapolation to ecosystem effects can be made with greater confidence, and thus a significant reduction in the assessment factor is possible.

An assessment factor of 50 is normally be applied when only one or two chronic NOECs have been determined from different taxonomic groups – usually fish or Daphnia - together with an algal toxicity NOEC. This may be reduced to 10 if there is evidence that the most sensitive species has been tested.

An assessment factor of 1000 for acute data is highly conservative. Indeed, ECETOC uses a factor of 200, while the US EPA uses a factor of 100 in these circumstances. The reason GPS proposes a factor of 1000 is to ensure that all substances with the potential to cause adverse effects are identified in the assessment. It assumes that each of the uncertainties identified in the above table contributes to the overall uncertainty. Nevertheless, a reduced factor can be used if the following justifications are provided:

- Information to suggest that the lowest L(E)C50 is from a group likely to represent the most sensitive species (not just the most sensitive tested);
- Information from structurally similar compounds or elsewhere, to suggest that the acute to chronic toxicity ratio is likely to be low;
- Information to suggest that the substance acts in a non-specific or narcotic manner, with little inter-species variation in toxicity;
- Information to suggest that the substance's release would be short-term, intermittent and would not persist in the environment;
- Any other information that would suggest that a lower assessment factor is appropriate.

Endpoint specific guidance

First refer to all information gathered in Section One. Where conclusions about the hazard endpoints cannot be drawn from available data, then the information can be drawn from (i) modelling²⁵, (ii) *in vitro* studies and (iii) *in vivo* studies.

In some cases, relevant data comes from occupational case studies. General considerations on evaluating data quality should always be applied when assessing human data. Alternatively, risk reduction measures beyond those already in place could reduce or eliminate the risk.

Modeling: several mathematical models exist. The following are the most commonly used models. Table 7 indicates which models can be used to estimate which hazard endpoints.

- T.E.S.T. Toxicity estimation software tool²⁶ (download software and training tools here: www.epa.gov/nrmrl/std/cppb/qsar/index.html#TEST)
- MultiCase²⁷ (commercial QSAR regression model that uses fragments and statistical rules to identify active and inactive fragments www.multicase.com/)
- DEREK²⁸ (Deductive Estimation of Risk from Existing Knowledge). LHASA Limited has been developing knowledge-based expert systems for toxicity and metabolism prediction. www.lhasalimited.org/. The Derek knowledge base covers a broad range of toxicological endpoints, but its main strengths lie in the areas of mutagenicity, carcinogenicity and skin sensitization.
- TOPKAT²⁹ (Toxicity Prediction by Computer-Assisted Technology) can be used for tests including physical/chemical, environmental fate, ecotoxicity, toxicity, irritation, mutagenicity, and sub chronic reproductive/developmental. www.accelrys.com/products/topkat/index.html

- HazardExpert³⁰ (module of Pallas software developed by CompuDrug Limited www.compudrug.com). It covers the following endpoints: oncogenicity, mutagenicity, teratogenicity, membrane irritation, sensitization, immunotoxicity, neurotoxicity. A further application of the program is prediction the toxicity of the parent compound and its metabolites by link with MetabolExpert system (another module of Pallas software).
- Tissue Metabolism Simulator (TIMES) integrates metabolic simulators and QSAR models for predicting toxicity of selected metabolites³¹. Can be used to predict skin sensitization, mutagenicity, chromosomal aberration and ER/AR binding affinities of chemicals, while accounting for metabolic activation (www.multicase.com).

Table 7: Appropriate models for assessing human health hazard endpoints

| Mathematical Model Human Health Hazard End Point | TEST | TOPKAT | HAZARD EXPERT | MULTICASE | DEREK | TIMES |
|---|------|--------|---------------|-----------|-------|-------|
| Acute Toxicity | ✓ | | ✓ | | | |
| Irritation / Corrosion | | ✓ | ✓ | | ✓ | |
| Sensitization | | ✓ | ✓ | | ✓ | ✓ |
| Mutagenicity / Genotoxicity | | ✓ | ✓ | | ✓ | ✓ |
| Repeat Dose Toxicity | | | | | | |
| Reproductive / Developmental Toxicity | | ✓ | ✓ | | | |

Human Health Hazard End Points

1. Acute toxicity

Assessing the acute toxicity potential of all chemicals from Tier 4 upwards is necessary in order to determine the adverse health effects that might occur following accidental or deliberate short-term exposure. The nature and severity of the acute toxicity effects are dependent upon factors such as the mechanism of toxicity and bioavailability of the chemical; the route and duration of exposure, and the total amount of chemical to which the person or animal is exposed.

The term acute toxicity describes adverse effects resulting from a single exposure or multiple exposures within 24 hours. Traditionally, acute toxicity tests in animals use mortality as the main observational endpoint in order to derive a LD(C)50 value (or alternatively NOEL or NOAEL in single administration studies)

The nature and reversibility of the toxic effects should always be considered. Several systemic effects may cause acute toxicity, but in many cases there will be little information on the cause of death or mechanism of action, with only limited information on clinical signs or pathological changes in specific tissues. Check the physico.-chemical characteristics of the chemical (e.g. dissociation constant, fat solubility, volatility): certain computer programs can predict the absorption, metabolism, distribution and excretion of a substance based on these parameters and offer information on possible target organs.

For chemicals showing high acute toxicity and where the exact dose cannot be defined because of test protocol limitations, it is important to perform a qualitative risk characterization. Under such circumstances strict Risk Management Measures (RMM) should apply (e.g., closed systems) in order to ensure exposure control.

- (i) **Modeling:** Quantitative Structure Activity Relationships (QSARs) are mathematical models used to predict toxicity measures from the physical and structural characteristics of chemicals (known as molecular descriptors). Acute toxicities (such as the concentration that causes half of a fish population to die) are one example of the toxicity measures that can be predicted from QSARs. Only a few (Q) SAR models capable of predicting acute toxicity (see Table 7 page 57):
- (ii) **In vitro methods:** As yet, no in vitro tests have been officially adopted by the EU or OECD to assess acute toxicity. However, a number are undergoing validation:
- BALB/c 3T3 NRU & normal human keratinocyte (NHK) NRU assay³² (http://iccvam.niehs.nih.gov/methods/acutetox/inv_nru_brd.htm).
 - Trans-epithelial resistance (TER), coupled with enhanced paracellular permeability (PCP)
 - CFU-GM.
- (iii) **In vivo methods:**

| Hazard | OECD – Test Guideline TG | US EPA OPPTS Test Guidelines |
|-----------------------|---|--|
| Acute Toxicity | 401 Acute Oral Toxicity 402 Acute Dermal Toxicity 403 Acute Inhalation Toxicity 420 Acute Oral toxicity - FDP 423 Acute Oral Toxicity - ATC 425 Acute Oral Toxicity: Up-and-Down 436 Acute Inhalation Toxicity - ATC | 870.1000 Acute Toxicity Testing- 870.1100 Acute Oral Toxicity (AOT) 870.1200 Acute Dermal Toxicity 870.1300 Acute Inhalation Toxicity |

2. Skin / Eye Irritation / Corrosion

Adverse changes (called “local effects”) at the site of first contact (skin, eye, mucous membrane/gastro-intestinal tract, or mucous membrane / respiratory tract) can be caused, irrespective of whether a substance can become systemically available. Substances that cause local effects after a single exposure can be categorised as irritant or corrosive substances, depending on the reversibility of the effects observed.

Skin / eye *corrosion* is the production of *irreversible* damage to the skin / eye. Skin irritation is the production of reversible damage (visible necrosis through the epidermis into the dermis) following the application of a test substance for up to 4 hours.

- A chemical predicted to be corrosive to the skin is automatically considered to be severely irritating to the eye, therefore testing for skin or eye irritation should not be performed for corrosive materials. However, a chemical may be corrosive when in contact with eyes or respiratory tract, even though it causes little or no skin irritation.
 - Strong acids or alkalis ($\text{pH} \leq 2$ and ≥ 11.5) are corrosive to the eyes and can be labelled as such without further testing
 - A severe skin irritant is likely to elicit similar characteristics on the eye and it can be labelled accordingly
- (i) **Modeling:** QSAR models can identify certain molecular structures that predict irritancy (e.g. ability to bind with protein). The occurrence of structural analogues that exhibit corrosion (or irritation) potential can be used to predict the effect of the substance. Structural alerts reflect chemical or biochemical reactivity that underlies the toxicological effect. Non-reactive chemicals, which lack alerts for reactivity, do not normally exhibit irritant or corrosive effects. However, irritant effects such as irritant contact dermatitis can occur in the case of exposure to organic solvents, which have de-fatting properties. The following QSAR models are capable of predicting irritation and corrosion: TOPKAT, HAZARD EXPERT, DEREK (see Table 7 page 57)

(ii) ***In vitro* methods:**

| Hazard | OECD – Test Guideline TG |
|-----------------------|--|
| Irritation eye / skin | <p>430 In Vitro Skin Corrosion: Transcutaneous Electrical Resistance Test</p> <p>431 In Vitro Skin Corrosion: Human Skin Model Test</p> <p>432 In Vitro 3T3 NRU Phototoxicity 435</p> <p>435 In Vitro Membrane Barrier Test Method for Skin Corrosion</p> <p>437 Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants</p> <p>438 Isolated Chicken Eye Test Method for Identifying Ocular Corrosives and Severe Irritants</p> |

(iii) ***In vivo* methods:** For skin and eye, the results of in vivo test results are relevant because the mechanisms of these local effects are considered to be the same in animals and humans. However, rabbits are the preferred species for skin tests: rats are not appropriate. For respiratory irritation, inter-species mechanism differences exist and as yet there are no validated tests for respiratory irritation.

| Hazard | OECD – Test Guideline TG | US EPA OPPTS | ISO Test Guidelines |
|-----------------------|--|--|---|
| Irritation eye / skin | <p>404 Acute Dermal Irritation / Corrosion</p> <p>405 Acute Eye Irritation / Corrosion</p> | <p>870.2400 Acute Eye Irritation</p> <p>870.2500 Acute Dermal Irritation</p> | <p>10993-3 Biological evaluation of medical devices - Part 10: Test for irritation and sensitization</p> |

3. Sensitization

A sensitizer is an agent that can cause an allergic response in susceptible individuals. Allergic responses can occur after skin, oral or inhalation exposure and are due to one of two mechanisms: immunological or non-immunological. For the purposes of this guidance document, only dermal exposure is considered since this is the most relevant. Following subsequent exposures to the skin, allergic contact dermatitis or atopic dermatitis may be provoked.

In some cases, available human data may be sufficient for the hazard assessment: for example diagnostic clinical studies, worker surveillance and case reports can be used when assessing the sensitization potential of chemicals. Good quality human data is normally preferable to animal data, however, a lack of positive findings in humans does not necessarily overrule quality animal data. Some animal test methods, such as the local lymph node assay (LLNA, OECD 429) and the guinea pig maximization test, can provide information on the dose-response relationships and thresholds for induction and elicitation in animals. The LLNA correlates relatively well with the human data on skin sensitization and can therefore be used for hazard assessment. When assessing the LLNA results, evidence for local toxicity and skin inflammation must be considered hand in hand with available information of skin irritation.

For skin sensitizers, the first approach should be the qualitative risk characterization based on potency categorization (strong/extreme and moderate sensitizers) and then defining the appropriate risk management measures (RMMs). If a NOAEL (no-observed-adverse-effect level) can be derived from the data available, the risk characterization for skin sensitization may be performed e.g. using the margin of exposure (MOE) approach. If a NOAEL is not available, the conclusion is that the risk cannot be characterized. In these cases, a strong emphasis is placed on controlling exposures to minimize the risks. Further data may be required to enable a more thorough risk characterization.

- (i) **Modeling:** (Q)SAR models are useful because the skin sensitization potential of a chemical is related to its ability to react with skin proteins to form covalently linked conjugates that are recognized by the immune system. In most cases, this is due to electrophilic reactivity of the chemical. QSAR models for respiratory sensitization are not yet available. The QSAR models applicable to sensitization are: DEREK, TOPKAT, HazardExpert and TIMES (see Table 7, page 57).
- (ii) **In vitro methods:** There are no officially adopted in vitro tests for skin or respiratory sensitization.
- (iii) **In vivo methods:** *In vivo* testing with corrosive chemicals at a concentration or dose that causes corrosivity should be avoided. Evidence for local toxicity, skin inflammation and available information of skin irritation should be considered when LLNA results are assessed. The LLNA has been shown to correlate relatively well with the human data on skin sensitization and may therefore be used for hazard assessment.

| Hazard | OECD – Test Guideline TG | US EPA OPPTS | ISO Test Guidelines |
|---------------|---|---------------------------------------|---|
| Sensitization | 406 Skin Sensitisation 429 Skin Sensitisation: Local Lymph Node Assay | 870.2600 Skin Sensitization | 10993-3 Biological evaluation of medical devices Part 10: Test for irritation and sensitization |

4. Mutagenicity and Genotoxicity

Mutagenicity refers to the induction of permanent transmissible changes in the amount or structure of the genetic material of cells or organisms. These changes may involve a single gene or gene segment, a block of genes or chromosomes.

Genotoxicity (sometimes used as synonym to mutagenicity) is a broader term which refers to processes that alter the structure, information content or segregation of DNA. Genotoxic changes are not necessarily always associated with mutations. Thus, tests for genotoxicity include tests which provide an indication of induced damage to DNA (but not direct evidence of mutation)³³.

The standard test for mutagenicity is the Ames test - an *in vitro* gene mutation study in bacteria. For many chemicals, the outcome of the Ames test can be predicted by structural alerts within the chemical. It is the company's decision whether to perform the Ames test or to accept the structural alert for positive predictivity, and therefore skip additional testing.

At higher tier stages (Tier 1 and 2) information on induction of gene mutations and/or chromosome aberrations *in vitro* and an *in vivo* assay for chromosomal aberrations (e.g., rodent bone marrow or peripheral blood micronucleus test) might be required. When assessing the test data, metabolic activation and physical-chemical properties of the test chemical need to be considered. Data on toxicokinetics is important when analyzing whether the test compound actually reached the target organ. Usually *in vivo* experiments and data obtained using mammalian cell lines is considered to be of higher significance. Relevance of indicator type of tests, such as DNA binding and sister chromatid exchange (SCE) assay is considered to be of lower relevance .

Exposure to mutagenic (genotoxic) chemicals has to be strictly controlled in order to prevent genetic damage. Especially for substances which are both genotoxic (damaging DNA, the genetic material of the cells) and carcinogenic (leading to cancer), it is generally assumed that even a small dose may have a potential adverse effect. In general, the advice given by risk assessors up until now in Europe has been to keep exposure to such compounds at the lowest possible level - ALARA principle ("as low as reasonably achievable").

- (i) **Modeling:** Non-test information about the mutagenicity of a substance can be derived in a variety of ways, ranging from simple inspection of the chemical structure through various read-across techniques, the use of expert systems, metabolic simulators, to global or local (Q)SARs. In many cases the accuracy of QSAR data will be sufficient to help, in other cases, the uncertainty may be unacceptable due to the severe consequences of a possible error. The following models can be used to assess mutagenicity and genotoxicity: DEREK; TOPKAT; HazardExpert and TIMES.

(ii) **In vitro methods:** Typically, *in vitro* tests are performed with cultured bacterial, human or other mammalian cells. The sensitivity and specificity of tests vary with different classes of substances and, if adequate data are available for the class of substance to be tested, can guide the selection of the most appropriate test systems. In order to detect mutagenic effects of substances that must be metabolically activated to become mutagenic, an exogenous metabolic activation system is usually added to *in vitro* tests.

| Hazard | OECD – Test Guideline TG | US EPA OPPTS Test Guidelines |
|-----------------------------|---|--|
| Mutagenicity / Genotoxicity | <p>471 Bacterial Reverse Mutation Test</p> <p>472 Genetic Toxicology: Escherichia coli, Reverse Assay</p> <p>473 In Vitro Mammalian Chromosome Aberration Test</p> <p>476 In Vitro Mammalian Cell Gene Mutation</p> <p>479 Genetic Toxicology: In Vitro Sister Chromatid Exchange assay</p> <p>480 Genetic Toxicology: Saccharomyces cerevisiae, Gene Mutation Assay</p> <p>481 Genetic Toxicology: Saccharomyces cerevisiae, Mitotic Recombination Assay</p> <p>482 Genetic Toxicology: DNA Damage and Repair, Unscheduled DNA Synthesis in Mammalian Cells In Vitro</p> | <p>870.5100 Bacterial Reverse Mutation Test</p> <p>870.5140 Gene Mutation in Aspergillus nidulans</p> <p>870.5300 In vitro Mammalian Cell Gene Mutation Test</p> <p>870.5375 In Vitro Mammalian Chromosome Aberration Test</p> <p>870.5500 Bacterial DNA Damage or Repair Tests</p> <p>870.5550 Unscheduled DNA Synthesis in Mammalian Cells in Culture</p> <p>870.5575 Mitotic Gene Conversion in Saccharomyces cerevisiae</p> <p>870.5900 In Vitro Sister Chromatid Exchange Assay</p> <p>870.5915 In Vitro Sister Chromatid Exchange Assay</p> |

(i) ***In vivo* methods:**

| Hazard | OECD – Test Guideline TG | US EPA OPPTS Test Guidelines |
|-----------------------------|---|--|
| Mutagenicity / Genotoxicity | 474 Mammalian Erythrocyte Micronucleus Test | 870.5195 Mouse Biochemical Specific Locus Test |
| | 475 Mammalian Bone Marrow Chromosome Aberration Test | 870.5200 Mouse Visible Specific Locus Test |
| | 477 Genetic Toxicology: Sex-Linked Recessive Lethal Test in <i>Drosophila melanogaster</i> | 870.5380 Mammalian Spermatogonial Chromosomal Aberration Test |
| | 478 Genetic Toxicology: Rodent dominant Lethal Test | 870.5385 Mammalian Bone Marrow Chromosomal Aberration Test |
| | 483 Mammalian Spermatogonial Chromosome Aberration Test | 870.5395 Mammalian Erythrocyte Micronucleus Test |
| | 484 Genetic Toxicology: Mouse Spot | 870.5450 Rodent Dominant Lethal Assay |
| | 485 Genetic Toxicology: Mouse Heritable Translocation Assay | 870.5460 Rodent Heritable Translocation Assays |
| | 486 Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells In Vivo | |

5. Repeated Dose toxicity

Repeated dose toxicity refers to toxic effects occurring after daily dosing with a chemical for 28 or 90 days, or a major portion of the lifespan in the case of chronic exposure. Effects include changes in morphology, physiology, growth, clinical chemistry or behavior. Tier 1 and 2 (high or medium exposure) substances require a repeat dose study conducted in rats by a route of administration appropriately reflective of potential human exposure.

Reproduction and developmental toxicity studies may provide information on general toxicological effects arising from repeated exposures. When reliable and relevant, the available positive epidemiological data is preferable over animal data. Ideally, the most likely route of real-life human exposure is the most appropriate test route. If this is not possible, then the oral exposure is the best test for repeated dose toxicity. The highest of three dose levels should be chosen with the aim to induce toxicity but not death. A descending sequence of dose levels should be selected to demonstrate any dose-related response and a no-observed-adverse-effect level (NOAEL) at the lowest dose level.

Typically, a NOAEL or LOAEL can be obtained from repeated dose toxicity studies. Intra- and inter-species assessment factors are normally applied. If adverse effects are not observed in a limit test (up to 1000 mg/kg of body weight), the chemical does not usually need to be assessed further. Emphasis should be given to N(L)OAEL(s) obtained from studies showing effects relevant to humans and studies with the most relevant experimental animal and duration for humans. Among studies of similar relevance, the study with the lowest N(L) OAEL should be chosen.

If experimental data allow, alternative methods for dose-response assessment can be applied, e.g. benchmark dose.

The outcome of these calculations may also be used in the risk characterization. Typically, further information on effects may be required when, after using all the relevant available data (including in particular data from toxicokinetics studies and human experience), it is not possible to extrapolate to the human route or duration of exposure.

- (i) **Modeling:** A review conducted by ECETOC on the use of (Q)SARs concluded that applicability of currently available (Q)SARs for chronic mammalian toxicity is limited as a stand-alone approach (ECETOC 2003).
- (ii) ***In vitro* methods:** No available alternatives to animal testing are currently accepted for regulatory purposes for detecting toxicity after repeated exposure.
- (iii) ***In vivo* methods:** Knowledge of the physico-chemical properties of a chemical essential to decide upon the appropriate administration route to be applied in experimental *in vivo* repeat dose toxicity studies, as well as to decide on exemption from testing in cases where testing is technically not possible. This might be the case if the substance:
 - Ignites in air at ambient conditions.
 - Undergoes immediate disintegration. In such a case the information requirements for the cleavage products should be assessed following an approach similar to that outlined in this document.
 - Is corrosive in the dose range of interest for the study. Also, for reasons of animal welfare such studies should be avoided.

The most appropriate data for hazard characterization and risk assessment comes from studies in experimental animals conforming to internationally agreed test guidelines. In some circumstances repeated dose toxicity studies not conforming to conventional test guidelines may also provide relevant information for this endpoint.

| Human Health Hazard | OECD – Test Guideline TG | US EPA OPPTS Test Guidelines |
|---------------------|---|--|
| Repeated Dose | <p>407 Repeated Dose 28-Day Oral Toxicity Study in Rodents</p> <p>408 Repeated Dose 90-Day Oral Toxicity Study in Rodents</p> <p>409 Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents</p> <p>410 Repeated Dose Dermal Toxicity: 90-Day</p> <p>411 Subchronic Inhalation Toxicity: 90-Day</p> <p>412 Sub acute Inhalation Toxicity: 28- Day Study</p> <p>413 Subchronic Inhalation Toxicity: 90-Day Study</p> <p>452 Chronic Toxicity Studies</p> | <p>870.3050 Repeated Dose 28-day Oral Toxicity Study in Rodents</p> <p>870.3100 90-Day Oral Toxicity in Rodents</p> <p>870.3150 90-Day Oral Toxicity in Nonrodents</p> <p>870.3200 21/28-Day Dermal Toxicity</p> <p>870.3250 90-Day Dermal Toxicity</p> <p>870.3465 90-Day Inhalation Toxicity</p> <p>870.3650 Combined Repeated Dose Toxicity with the Reproduction/Development Toxicity Screening Test</p> <p>870.4100 Chronic Toxicity</p> <p>870.4300 Combined Chronic Toxicity / Carcinogenicity</p> |

6. Reproductive / Developmental toxicity

Reproductive toxicity describes the adverse effects induced by a substance on adult sexual function and fertility, developmental toxicity in the offspring, and effects on or mediated via lactation. Reproductive toxicity is characterized by multiple diverse endpoints which relate to the impairment of male and female reproductive functions or capacity (fertility) and the induction of non-heritable harmful effects on the progeny (developmental toxicity).

The hazard potential for reproductive or developmental disorders must be established for chemicals with human exposure that may be present in the environment, at the workplace or in consumer products because the continuance of the species is dependent on the integrity of the reproductive cycle and reproductive or developmental disorders are clearly of serious concern to individuals. The information requirement for reproductive toxicity data only applies to Tier 1.

The assessment must distinguish between a *specific effect* on reproduction and an adverse reproductive effect which is a *non-specific consequence* to general toxicity. Usually, reproductive toxicity effects are considered to be due to underlying dose-response mechanisms. As a result, a NOAEL or LOAEL value should be provided from the available data. However, the threshold dose for specific aspects of reproductive toxicity is not always easy to identify. In the rare case that a NOAEL has been derived from well-reported and reliable human data, it should be used for risk characterization - but usually a value from a study conducted in animals will be used.

In cases where appropriate testing has been conducted at dose levels up to the maximum required under the standard test guidelines (for example OECD 421, and no adverse effects on reproduction are observed - it can be concluded that reproductive toxicity is unlikely to be of concern, and calculation of a MOS is unnecessary.

Particular attention should be given to the relationships between dose/concentration and adverse effects on reproduction and other systemic toxicity. The developing offspring should be a focus of attention in the MOS assessment because the effects in the mother may be mild and reversible, attracting a low level of concern, whereas the effects in the offspring at similar exposure levels might have more serious long-term consequences. Epidemiological studies, conducted in the general population or occupational cohorts, may provide information on reproductive toxicity. Although not aimed directly at investigating reproductive toxicity, repeated-dose toxicity studies may reveal effects on reproductive organs in test animals.

- (i) **Modeling:** QSAR can offer approaches to assess reproductive toxicity by extrapolating or interpolating across a homologous series or category. There are a large number of potential targets/mechanisms associated with reproductive toxicity that, on the basis of current knowledge, cannot be adequately covered by a battery of models. Unlike some toxicological endpoints for which specific structural alerts have been identified (e.g. mutagenicity, sensitization), there are currently no formal criteria to identify structural alerts for reproductive toxicity. Therefore, a negative result from current QSAR models cannot be interpreted as demonstrating the absence of a reproductive hazard unless there is other supporting evidence. Appropriate models include TOPKAT and Hazard Expert.
- (ii) ***In vitro* methods:** Currently, there is no officially adopted EU or OECD test guideline for *in vitro* tests relevant to reproductive toxicity. Three tests have recently been subjected to an extensive multicentre validation study in the EU and declared to be scientifically validated tests for use in assessing embryotoxic potential according to the European Centre for the Validation of Alternative Methods (ECVAM) procedures. However, at present, *in vitro* approaches have many limitations: for example the lack of capacity for biotransformation of the test substance³⁴. Consequently, no firm recommendations can be made for the exclusive use of *in vitro* methods in a testing strategy for reproductive toxicity. The combination of assays in a tiered or battery approach may improve predictivity, but the *in vivo* situation remains more than the sum of the areas modelled by a series of *in vitro* assays.
 - Embryonic stem cell test³⁵
 - Limb bud micromass culture³⁶
 - Whole embryo culture³⁷

(iii) ***In vivo*** methods:

| Human Health Hazard | OECD – Test Guideline TG | US EPA OPPTS Test Guidelines |
|------------------------------|--|---|
| Reproductive Toxicity | 414 Prenatal Developmental Toxicity | 870.3550 Reproduction / Development Toxicity Screening Test |
| | 415 One-Generation Reproduction | 870.3650 Combined Repeated Dose Toxicity with the Reproduction / Development Toxicity Screening Test |
| | 416 Two-generation Reproduction | 870.3700 Prenatal Developmental Toxicity Study |
| | 421 Reproduction / Developmental Screening Test | 870.3800 Reproduction and Fertility Effects |
| | 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test | |
| | 440 Uterotrophic Bioassay in Rodents | |
| | 441 Hershberger Bioassay in Rats | |

Environmental Hazard End Points

1. Aquatic toxicity

Aquatic toxicity refers to intrinsic property of a chemical to be detrimental to an aquatic organism when the organism is exposed to the chemical in the short-or-long term. Waterborne exposure to chemicals is considered the predominant route, but aquatic organisms may also be exposed via food (e.g. to lipophilic chemicals). A distinction is made between short-term (so-called acute) effects and long-term effects (chronic).

Acute toxicity is based on the short term exposure of aquatic organisms to the test chemical(s). Exposure can range from hours to a few days (relatively short in comparison to the duration of the life-cycle of the organisms). Effects are normally expressed as median lethal or effect concentrations (L/EC50), which is the test concentration at which 50% of the organisms is affected or at which 50% effect is measured for a specifically defined endpoint (e.g. growth rate effects on algae).

Chronic toxicity refers to aquatic organisms exposed to chemicals for a prolonged period. Exposure (test) duration can vary widely, depending on the species used, but is generally a relatively long duration within the total length of the life cycle. Such chronic effects include a range of endpoints such as survival, growth and reproduction.

The most frequently used parameter is the highest tested concentration where an effect has not been observed. All available aquatic toxicity data needs to be evaluated in the hazard assessment and, if suitable, used to derive an overall Predicted No-Effect-Concentration (PNEC) for the aquatic compartment. A PNEC is a concentration below which an unacceptable effect will probably not occur. In principle, the PNEC is calculated by dividing the lowest short-term L(E)C50 or long-term NOEC value by an appropriate assessment factor. The assessment factors reflect the degree of uncertainty in extrapolation from laboratory toxicity test data for a limited number of species to the 'real' environment. Assessment factors applied for long-term tests are smaller, as the uncertainty of the extrapolation from laboratory data to the natural environment is reduced. For this reason long-term data are preferred to short-term data.

For a chemical to be safe, the PNEC concentration has to be higher than the Predicted Environmental Concentration (PEC). The PEC is the concentration one expects to find in the environment. The assessment has to be repeated for each relevant environmental compartment, such as wastewater treatment plants, surface water, sediment and soils. The PEC/PNEC ratio is used as an indicator of risk. If the PEC is lower than the calculated PNEC (ratio below 1) no adverse effects are anticipated and the use of the chemical in the environment is safe.

(i) **Modeling:**

- Estimation Program Interface (EPI) Suite: The EPI Suite is a Windows-based suite of toxicity, physical/chemical property and environmental fate estimation programs developed by the EPA's Office of Pollution Prevention Toxics and Syracuse Research.
- QSAR Application Toolbox: The Toolbox is a software application intended to be used by Governments, chemical industry and other stakeholders in filling gaps in (eco)toxicity data needed for assessing the hazards of chemicals. The Toolbox incorporates information and tools from various sources into a logical workflow. Crucial to this workflow is grouping chemicals into chemical categories³⁸.

(ii) ***In vitro* methods:** Currently there is no officially adopted EU or OECD test guideline for *in vitro* tests

(iii) ***In vitro* methods:**

| Hazard | OECD | US EPA | ISO |
|----------------|--|---|---|
| Acute | <p>201 Alga, Growth Inhibition</p> <p>202 Daphnia sp. Acute immobilisation Test</p> <p>203 Fish, Acute Toxicity</p> <p>209 Activated Sludge, Respiration Inhibition</p> <p>221 Lemna sp. Growth Inhibition Test</p> | <p>850.1010 Invertebrate Acute Toxicity</p> <p>850.1020 Gammarid Acute</p> <p>850.1025 Oyster Acute</p> <p>850.1035 Mysid Acute T</p> <p>850.1045 Penaeid Acute</p> <p>850.1055 Bivalve Acute</p> <p>850.1075 Fish Acute</p> <p>850.1085 Fish Acute</p> | <p>8692 Fresh water algal growth inhibition</p> <p>6341 Acute toxicity test</p> <p>7346 -1,-2,-3 Acute lethal toxicity freshwater fish</p> <p>20079 Duckweed growth inhibition test</p> |
| Chronic | <p>204 Fish, Prolonged Toxicity Test: 14-Day Study</p> <p>210 Fish, Early-Life Stage</p> <p>211 Daphnia magna Reproduction</p> <p>212 Fish, Short- term Toxicity Test</p> <p>215 Fish, Juvenile Growth</p> <p>229 Fish Short Term Reproduction Assay</p> <p>230 21-Day Fish Assay: A Short Term Screening for Oestrogenic and Androgenic Activity, and Aromatase Inhibition</p> <p>231 Amphibian Metamorphosis Assay</p> | <p>850.1300 Daphnid Chronic Toxicity Test</p> <p>850.1350 Mysid Chronic Toxicity Test</p> <p>850.1400 Fish Early-Life Stage Toxicity Test</p> <p>850.1500 Fish Life Cycle Toxicity</p> | <p>10229 Prolonged toxicity of substances to freshwater fish</p> <p>10706 Determination of long term toxicity to Daphnia magna Straus</p> <p>12890 Embryo-larval toxicity to freshwater fish</p> |

2. Degradation, bioaccumulation

Degradation is the loss or transformation of a chemical in the environment, due to abiotic (non-biological) or biotic (bio-degradation) processes. Abiotic degradation can occur by physico-chemical processes such as hydrolysis, oxidation and photolysis. Biodegradation can occur either in the presence of oxygen (aerobic biodegradation) or in the absence of oxygen (anaerobic biodegradation).

Assessment of degradation and persistency is based on data obtained from standardized tests for ready biodegradability and hydrolysis. Results of tests simulating the biodegradation in water, aquatic sediment and soil are considered higher Tier data that can also be used for these purposes. Other types of test data that may be considered in an assessment of the potential environmental hazard or risk include sewage treatment plant (STP) simulation data, inherent biodegradability, anaerobic biodegradability, biodegradability in seawater and abiotic transformation.

In determining which degradation data are required, consideration should be given to the partitioning behavior of the chemical and its release or emission pattern. The n-octanol / water partition coefficient (K_{ow}) is one of the key physico-chemical parameters. It is used to estimate environmental partitioning, absorption, bioavailability, bioconcentration, bioaccumulation and also human toxicity and eco-toxicity. K_{ow} does not need to be determined if the substance is purely inorganic. K_{ow} is defined as the ratio of the equilibrium concentrations of a dissolved substance in a 2-phase system consisting of the largely immiscible (lipophilic) solvents n-octanol and water. K_{ow} is moderately temperature-dependent and typically measured at 25°C. The bioconcentration or bioaccumulation factor (BCF/BAF) measures the potential for a chemical to accumulate in living organisms relative to its concentration in the surrounding environment and is estimated using calculations based on K_{ow} .

Chemical substances having a BCF or BAF >1000 have a tendency to accumulate in organisms. Persistent, bioaccumulating and toxic (PBT) chemicals are priority pollutants and pose potential risks to humans and ecosystems³⁹. The EU criteria for PBT chemicals are listed below:

Table 8: EU criteria for PBT chemicals

| Criterion | PBT criteria | vPvB criteria |
|-----------|--|---|
| P | Half-life > 60 d in marine water or > 40 d in freshwater or half-life > 180 d in marine sediment or > 120 d in freshwater sediment <i>Or not readily or inherently biodegradable</i> <i>Or predicted biodegradability in a time frame of weeks-months</i> | Half-life > 60 d in marine or freshwater or > 180 d in marine or freshwater sediment <i>Or not readily or inherently biodegradable</i> <i>Or predicted biodegradability in a time frame of weeks-months</i> |
| B | BCF > 2,000 Or low Kow > 1.5 | BCF > 5,000 Or log Kow > 5 |

Alternatively the US EPA has established slightly different PBT criteria and developed a PBT Profiler as a voluntary screening tool to identify Pollution Prevention opportunities for chemicals without experimental data⁴⁰.

- (i) **Modeling:** In addition to the EPI and CATABOL models described under aquatic toxicity above, CATABOL is also appropriate: CATABOL predict persistency, biodegradation, etc. Predicts the magnitude and physicochemical and toxic endpoints of stable degradants across biodegradation pathways of the chemicals.

(ii) **Methods:**

| Environmental fate | | | |
|---------------------------|--|--|---|
| | 111 Hydrolysis function of pH | 835.2110 Hydrolysis as a Function of pH | 7827 Aerobic biodegradability of organic compounds |
| | 302A Inherent Biodegradability: Modified SCAS Test | 835.2120 Hydrolysis | 9439 Aerobic biodegradability of organic compounds in aqueous medium |
| | 302B Inherent Biodegradability: EMPA Test | 835.2130 Hydrolysis as a Function of pH and Temperature | 10707 Aerobic biodegradability of organic compounds |
| | 302C Inherent Biodegradability: MITI Test (II) | 835.2210 Direct Photolysis Rate in Water by Sunlight | 9408 Aerobic biodegradability of organic compounds in aqueous medium |
| | 303 Simulation Test – Aerobic Sewage Treatment Activated Sludge Units | 835.2240 Photodegradation in Water | 14593 Aerobic biodegradability of organic compounds in aqueous medium |
| | 304A Inherent Biodegradability in Soil | 835.2310 Maximum Direct Photolysis Rate in Air from UV/ Visible Spectroscopy | 9887 Aerobic biodegradability - Semi-continuous activated sludge method (SCAS) |
| | 305 Bioconcentration: Flow-Through Fish Test | 835.2370 Photodegradation in Air | 11733 Elimination and biodegradability of organic compounds in an aqueous medium - Activated sludge simulation test |
| | 306 Biodegradability in Seawater | 835.2410 Photodegradation in Soil | 14592-1 Aerobic biodegradability Shake-flask batch |
| | 307 Aerobic and Anaerobic Transformation in Soil | 835.3100 Aerobic Aquatic Biodegradation | 1622 Determination of biodegradability in the marine environment |
| | 308 Aerobic and Anaerobic Transformation in Aquatic Sediment Systems | 835.3110 Ready Biodegradability | 11266 Soil quality – Guidance on biodegradation of organic chemicals in soil |
| | 309 Aerobic Mineralisation in Surface Water – Simulation Biodegradation Test | | |
| | 310 Ready Biodegradability - CO ₂ in sealed vessels | | |

**Environmental
fate**

- 301** Ready Biodegradability
- 301A** DOC Die-Away Test
- 301B** Co₂ Evolution Test
- 301C** Modified MITI Test (I)
- 301D** Closed Bottle Test
- 301E** Modified OECD Screening Test
- 301F** Manometric Respirometry Test

Dose Descriptors

- **LD50 (Lethal Dose x %):** The LD50 corresponds to the dose of a tested substance causing 50 % lethality during a specified time interval.
- **LC50 (Lethal Concentration x %):** The LC50 corresponds to the concentration of a tested substance causing 50 % lethality during a specified time interval.
- **T25:** The chronic dose rate that will give 25% of the animals' tumors at a specific tissue after correction for spontaneous incidence, within the life time of that species
- **No-observed-adverse-effect level (NOAEL):** The highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered adverse effects.
- **Lowest-observed-adverse-effect level (LOAEL):** The lowest exposure level at which there are biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group.
- **No Observed Adverse Effect Concentration (NOAEC):** The highest tested concentration at which there are no statistically significant increases in the frequency or severity of adverse effects between the exposed population and an appropriate control group, some effects may be produced at this level, but they are not considered adverse or precursors of adverse effects.
- **Benchmark Dose (BMD) or Concentration (BMC):** A dose or concentration that produces a predetermined change in response rate of an adverse effect (called the benchmark response or BMR) compared to background.

Guidance on Dose-Response

A safe human dose is usually estimated by extrapolating animal data to humans. In animal tests, the incidence of effects deriving from a target substance is obtained after exposure of animals to the fixed amount of the chemical for a certain period. This rate indicates the severity of effects of the chemical. The dose found to be safe for animals is used to estimate a safe human dose. The effects of chemical substances on living organisms are very complex.

This supplementary information is limited to presenting a simplified evaluation that estimates the effects of acute and repeated exposure to a chemical.

A dose-response curve defines the relationship between dose and response based on the following assumptions:

Response proportionally increases as dose increases and there is a threshold dose - a dose below which there is no effect.

Several issues must be considered in the evaluation of dose-response assessments.

- **Experimental Model:** It is neither feasible, nor ethical to expose human subjects to serial doses of potential hazardous chemicals to measure adverse effects, and thus an experimental model is used. The validity of the experimental model (animal) is critical to extrapolate effects in animals to effects in humans.
- **Physiology of target system:** While the dose-response relationship may characterize an association between two variables (dose of chemical agent and response), the response or adverse effect is most likely the result of many processes that are interdependent and necessary for maintaining homeostasis of the tissue, organ, or function being studied.

- **Homeostasis:** Homeostasis is the maintenance of a biological system that is achieved by numerous feedback mechanisms. For an individual cell, intracellular pH, ion balance, water balance and many other processes are regulated within a narrow range. Larger systems such as tissues, organs and entire organisms also maintain homeostasis of hormone levels, blood cell counts, body temperature, metabolic rates and many other processes.
It is necessary to understand how perturbations in the homeostasis of a system (i.e. endocrine system) can result in disease or dysfunction. Quantification of these changes in homeostasis may be reflected in the dose-response relationship.
- **Individual Susceptibility:** It is commonly known that many diseases are affected by both modifiable risk factors (lifestyle, diet, socio-economic factors) as well as non-modifiable factors (genetics, gender, race, age). These inter-individual factors may affect the susceptibility of some populations to the effects of toxicants. These factors should be considered in the dose-response relationship.

Assessment Factors

Table 9: ECHA Guidance - Assessment Factors

| Assessment Factors – accounting for differences in: | | Systemic effects | Local effects |
|---|---|-------------------|---------------|
| Interspecies | • Correction for differences in metabolic rate (allometric factor) | 4 (rat → humans) | 1 |
| | • “remaining differences” | 7 (mice → humans) | 1 |
| | | 2.5 | 2.5 |
| Intraspecies | • Worker | 5 | 5 |
| | • General population | 10 | 10 |
| Time extrapolation | • Sub-acute to sub-chronic | 3 | 3 |
| | • Sub-chronic to chronic | 2 | 2 |
| | • Sub-acute to chronic | 6 | 6 |
| Route to route extrapolation | • Oral to inhalation | 2 | |
| | • Inhalation to oral | 1 | |
| | • Dermal to oral | 1 | |
| | • Oral to dermal | 1 | |
| | • Dermal to inhalation | case-by-case | |
| | • Inhalation to dermal | case-by-case | |
| Dose-response/ severity of effect | • Reliability of the dose-response, LOAEL/NAEL extrapolation and severity of effect | ≥1 | ≥1 |
| Quality of whole data base | • Completeness and consistency of the available data | ≥1 | ≥1 |
| | • Reliability of alternative data | ≥1 | ≥1 |

Examples for DNEL calculation

Step 1: Identify dose descriptor

a) **Dermal Irritation (local effect)**

Dose descriptor:

- NOAEL 50 mg/kg bw/ day

Rationale for selection of dose descriptor:

- Skin irritation observed at higher doses

b) **Adrenal gland changes (systemic effect)**

Dose descriptor:

- NOAEL 10 mg/kg bw/day

Rationale for selection of dose descriptor:

- Adverse changes to adrenal glands observed at higher doses

c) **Developmental effects (systemic effect)**

Dose descriptor:

- NOAEL 50 mg/kg bw/day

Rationale for selection of dose descriptor:

- Developmental effects observed at higher doses

Step 2: Decide on threshold / non-threshold (Mode of Action)

Dermal Route, Local & Systemic Effects

Irritation

- Dose-response information supports threshold
Adrenal Effects
- Dose-response information supports threshold
Developmental Effects
- Dose-response information supports threshold

Step 3: Modify Point of Departure

Irritation (Local)

- No modification needed

Adrenal (Systemic) Effects

- Substance-specific data indicates dermal absorption is 2x less in humans than rats

$$10 \frac{\text{mg}}{\text{Kg}} \times \frac{1}{0.5} = 20 \frac{\text{mg}}{\text{kg}}$$

Developmental (Systemic) Effects

- Substance-specific data indicates dermal absorption is 2x less in humans than rats

$$50 \frac{\text{mg}}{\text{Kg}} \times \frac{1}{0.5} = 100 \frac{\text{mg}}{\text{kg}}$$

Step 4: Apply Assessment Factors

| | Irritation | Adrenal effects | Developmental effects |
|------------------------|---------------------------|-----------------------------|-----------------------------|
| (modified) NOAEL | 50 | 20 | 100 |
| Rational | AF | AF | AF |
| Intraspecies | 5 | 5 | 5 |
| Interspecies | 1 | 10 | 10 |
| Duration | 2 | 2 | 2 |
| POD | 3 | 3 | 3 |
| Total (AF) | 5 x 1 x 2 x 3 = 30 | 5 x 10 x 2 x 3 = 300 | 5 x 10 x 2 x 3 = 300 |
| DNEL mg/kg/bw/d | 1.7 | 0.1 | 0.3 |

Step 5: Select leading adverse effect

- Other routes of exposure are not relevant
- Dermal route to inhalation route conversion is not appropriate for local effects
- The DNEL-dermal-long term-local is 1.7 mg/kg bw/day
- The DNEL-dermal-long term-systemic is 0.1 mg/kg bw/day

Examples for DMEL calculation

Step 1: Identify dose descriptor

- T25 as basis for POD = 250 ppm

Step 2: Decide on threshold / non-threshold (Mode of Action)

- Non-threshold carcinogen

Step 3: Modify Point of Departure

- No modification needed

Step 4: Apply assessment factors

| | Cancer |
|---------------------------|------------------------------------|
| (modified) NOAEL | 250ppm |
| Rational | AF |
| Intraspecies | 5 |
| Interspecies | 1 |
| Duration | 1 |
| Quality of data base | 1 |
| Severity of effect | 10 |
| Total (AF) | 5 x 1 x 1 x 1 x 1 x 10 = 50 |
| DMEL ppm/kg/bw/d | 0.5 ppm |

SECTION TWO IMPLEMENTATION

STEP 6: ASSESS EXPOSURE

Exposure is a determinant of the effect of chemicals on humans and the environment, and an important factor in risk assessment. Exposure is defined as contact over time and space between a person and one or more biological, chemical or physical agent⁴¹. Exposure assessment identifies and defines the exposures that occur – or are anticipated to occur – in human populations and the environment throughout a products life cycle.

The process of a chemical entering the body can be described in two steps: contact (exposure), followed by actual entry (crossing the boundary). Absorption leads to the availability of an amount of the chemical to biologically significant sites within the body (internal dose). Exposure to a particular substance should normally be understood as external exposure.

In order to produce a meaningful risk assessment it is important to take into account the uncertainties associated with data on exposure: How realistic and how representative is the exposure assessment? Exposure estimates are affected by many things including: sampling and measurement techniques; selection of measured data; size of data sets; use of modeled data; reliability of models used; selection of exposure factors for modeling; the quantity and quality of contextual information; the definition and description of exposure scenarios.

The aim is for the exposure estimate to be as accurate as possible, but to apply the worst case approach where there is insufficient information to be on the safe side.

Prior to embarking on Step 6, it is important to take into account the considerations below:

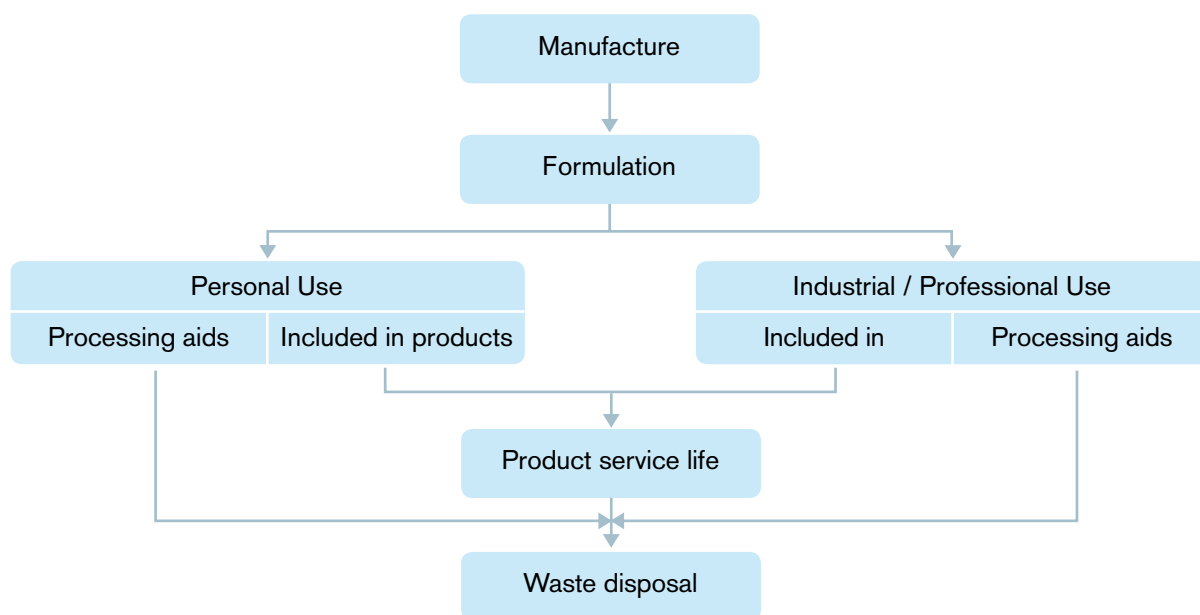
General Considerations when undertaking the Exposure Assessment

- 1. Perform step-wise assessment:** Exposure is first evaluated under normal exposure conditions. This is performed assuming a worst case scenario, and complete when the results of risk characterization indicate that the risk from the substance is under control. When the assessment in this first step does not show that the risk is adequately managed, it is repeated by reexamination of individual exposure information obtained from measurements (or refining the hazard assessment) and by reviewing the risk management measures until the results confirm that the risk is controlled.

2. **Take existing Risk Management Measures into account:** Risk management measures such as exposure prevention and environmental emission reduction are already in place in the workplace for most chemical substances that are manufactured and used and are on the market. Water containing waste chemicals after they have been used by consumers is processed at public sewage plants. This means that chemicals used by consumers generally undergo some form of risk management before being released into the environment. An exposure assessment requires the exposure scenarios to take into account the operational conditions of products in accordance with their potential applications, as well as the existing risk management measures that reduce and prevent exposure to chemicals.
3. **Examine the entire product life cycle:** Exposure assessment should target the entire product life cycle of a given chemical. As a result, information on the handling of products in the supply chain and information on products used in the manufacturing process is needed. This is a non-binding target because gathering information downstream of initial users may be difficult in some cases.

The flow chart below outlines the life cycle of a chemical: chemical manufacturers should include each aspect in the life cycle analysis of their products. Companies purchasing chemicals as raw materials to be processed or used in preparations should survey uses and disposal routes by downstream users in addition to their own internal handling.

Figure 4: The life cycle of a chemical



SECTION TWO IMPLEMENTATION

STEP 6: ASSESS EXPOSURE

4. Consider exposure to workers, consumers and the environment:

Workers may be exposed to chemicals in the workplace. In general, workers are a more homogenous group than consumers – but their potential exposures are likely to be greater. A consumer product is a product that can be purchased from retail outlets by members of the general public. Because the general public contains a wide variety of sub-populations – some are more susceptible than others to chemical risks (for example, the very young, the very old, those with health disorders or genetic susceptibilities) and therefore particular attention needs to be paid to potential exposures to susceptible sub-populations. Estimation of environmental exposure is complex and should include local, regional, inland and marine risks.

How to do the Exposure Assessment?

- Collect information on chemical properties
- Collect information on the uses and the typical operating conditions and risk management (exposure control) measures applied
- Set up an Exposure Scenario for each use
- Estimate exposure for each scenario, using estimating tools (e.g. ECETOC TRA) or measured data

The guidance below describes this process, first for human exposure assessment, and then for environmental exposure assessment.

Human Exposure Assessment

1. Collect Information on chemical properties

Part of the information needed has already been gathered in the Tier requirements of the Base Set of information. For other sources of information please refer to the tables in supplement to Step 1 (page 16). The table below summarizes the relevant determinants required in order to conduct an exposure assessment:

Table 10: Information on chemical

| Category | Examples of exposure determinants | Use descriptors |
|------------------------------|--|-----------------|
| I: Physical properties | Molecular weight, physico-chemical properties (e.g. Vp, Pow), stability | |
| II: Product information | Life cycle, applications, production volume, information on supply chain | SU |
| III: Product characteristics | Composition, shape, physical state, handling volume, packaging | PC, AC |

2. Collect Information on operating conditions (OCs), uses and risk management measures (RMMs)

Information on operating conditions (OC), uses and implemented risk management measures (RMMs) can be gathered by using the sources provided in <http://cefic.org/en/reach-for-industries-libraries.html>.

However, you should also ask your marketing and sales departments, the facility experts, your customers and sector branches for additional information. OCs and RMMs are closely related and are normally communicated in combination. Typically OC / RMM are defined by specific sectors (see page 21).

Table 11: Information on operating conditions and risk management measures

| | | |
|-----------------------------------|---|-----------|
| IV: Operational conditions (OC) | Process, handling volume, period/frequency, operational conditions, facilities | PROC, ERC |
| V: Risk management measures (RMM) | Exposure prevention measures (protective equipment, local ventilation/exhaust emission), effluent treatment methods | |
| VI: Environmental characteristics | Surrounding environment, spatial dimension, environmental conditions (destination of emission/effluent) Waste water treatment, sludge disposal | ERC |
| VII: Others | Regulations relevant to the product or substance the product contains, MSDS, technical documents | |

SECTION TWO IMPLEMENTATION

STEP 6: ASSESS EXPOSURE

3. Set up an Exposure Scenario

In order to set up Exposure Scenarios, you will need to consider the main chemical use situations and its use descriptors and use categories:

Collect information on uses

Uses can be categorized in several ways to begin to sort the nature of exposure. One high level approach is to look at grouping uses according to the degree of control of exposure:

- i. Transported isolated intermediate used/stored off site*
Such substances are likely to be used by a limited number of companies who are used to routinely handling chemicals and are likely to have procedures in place to ensure emissions and exposures remain well controlled. These include engineering control technologies and high standards of operator training and related work practices. In addition, the considerable workplace legislation in place ensures minimum standards. Therefore, it is very likely that emissions and exposures are well controlled.
- ii. Chemical is included into or onto a matrix*
Such chemicals have a similar emission patterns to the off-site intermediate, but has the potential for exposure to a wider population due to subsequent use of the matrix into which it is included. This means there are theoretically higher increased environmental emissions and human exposures compared to process chemicals. Whether the chemical can be released from the matrix over time or under expected conditions needs to be considered.
- iii. Non-dispersive use - Professional (industry point sources)*
These chemicals are likely to be used both by companies familiar with handling chemicals and by organizations who are not. Although some companies will have put in place systems and procedures to ensure emissions and exposures remain controlled, others do not. As a result, emissions and exposures may be low in some areas of use and higher in others, depending on the industrial or professional market(s) using the chemical.

iv. Wide dispersive use

Such chemicals are likely to reach consumers and we can assume it will be released into the environment during or after use. However, the chemicals in consumer products are encountered usually at low concentrations; is used less frequently and in much smaller volumes than industrial uses.

In addition, humans who are exposed are very different to those in industry in that (a) the exposed population is more diverse (for example, it includes the young, sick and elderly), (b) the exposure is very often to a mixture of chemicals (as consumer products are usually preparations) and not to single chemicals, and (c) because the public is not specifically trained to use a consumer product in the specified manner, public use of consumer products may be used in ways that were not originally intended or for which they are not intentionally sold.

Although consumer exposures are invariably lower than workplace exposures, there is less confidence in exposure estimates.

Many chemicals may be used in more than one main use category. For simplicity, the main use, which leads to the highest exposure potential, is used. This is a conservative approach that will, in some cases lead to an overestimate of potential exposure.

SECTION TWO IMPLEMENTATION

STEP 6: ASSESS EXPOSURE

Use Descriptors and Use Categories

Use Categories describe the function of the chemical and links actual handling and use of the chemical with general exposure scenarios and models that have been reported by the industry, the supply chain and research organizations. They can differ from region to region so it is important to specify which region of origin of the chemical. If a regional approach is in place, companies should follow it.

Different use descriptor systems include:

- EU NACE codes for sectors of use⁴²
http://ec.europa.eu/competition/mergers/cases/index/nace_all.htm
- OECD Use patterns (Main Pattern, Industrial and Use Category)⁴³
http://www.oecd.org/document/46/0,3343,en_2649_34373_2412462_1_1_1_1,00.html
- Updated REACH / IUCLID use descriptor system (see page 101)
- Harmonized codes for US and CND (36 Industrial functions and 40 Consumer and Product codes)

Tools to collect and establish use descriptors / scenarios can be found in the Supplement, starting page 104). General information on production and use is available through EPA – from its IUR database, IRIS, and its exposure factors handbooks. The Alliance for Chemical Awareness (www.chemicalawareness.org) has a library of resources on determining chemical exposures. Downstream trade associations can also provide information.

Use Descriptors under REACH: To structure the large number of different uses of substances and preparations present in the different industry sectors ECHA has developed a system to describe uses in a standard and structured way. This so called “Use Descriptor System” is based on five separate categories. Each category has pre-defined descriptors which in combination with each other form a brief description of use.

Use descriptors used in the chemical safety assessment (CSA) guidance of the ECHA are as follows:

- Sector of Use (SU)
- Product Category (PC)
- Article Category (AC)
- Process Category (PROC)
- Environmental Release Category (ERC)

Box 9 below provides examples of **Use Categories** to be employed where no regional guidance exists. If the list does not adequately describe the use, a detailed description should be provided. Where a variety of uses exist, an estimation of different uses in percentage terms should be given. References and information sources should be provided for each data element.

Box 9: Use Categories

- Colouring Agents
- Intermediates
- Solvents
- Adhesives
- Cleaning/washing agents
- Fertilizers
- Impregnation agents
- Surface active

Estimate Exposure for that scenario, using estimating tools

Exposure assessment estimates the levels of

- 1) occupational exposure to workers in manufacturing, processing, use, and disposal of chemicals;
- 2) consumers in the consumption of finished products, and
- 3) exposure of non-human organisms and humans, via the environment, in manufacturing and usage, and after disposal of chemicals.

NOTE: Exposure assessment is based on representative measured data or model calculations. Information on substances with analogous use and exposure patterns or analogous properties should be taken into account where appropriate. This is a complex approach and should be performed by a scientific expert.

SECTION TWO IMPLEMENTATION

STEP 6: ASSESS EXPOSURE

Workplace Exposure

1. Identification of relevant uses (e.g. PROCs)
2. Compile all available exposure data e.g. workplace measurements ideally linked to certain OCs / RMMs
3. For use categories with no exposure data available use a calculation tool such as tier 1 tier 1 ECETOC TRA (consider duration of activity, ventilation, PPE, etc)
4. If calculation of DNEL / Exposure ratios indicated risk (Step 7 RCR >1), obtain more detailed exposure information and assess again with tier 2 tools (e.g. RiskOfDerm, Stoffenmanager, ART)

In the workplace, exposure to chemicals occurs via three exposure routes: inhalation, dermal contact and oral intake. Each exposure route must be calculated separately by using either measured data or predictive estimation models. For occupational exposure, the following stages of the life cycle of a substance are mainly relevant:

- Manufacturing: Chemical synthesis of the substance and its use as intermediate
- Formulation: Mixing and blending into a preparation;
- Industrial use: Application of the substance, preparation/product in an industrial process;
- Professional use: Application of preparations/products in skill trade premises.

In order to enable proper worker exposure estimation the following types of information are needed:

- Where and how the substance is used e.g. process description
- The composition of mixtures, formulations and products;
- Physical form in which the substance is handled (e.g. powder, pellets, liquid);
- Description of tasks, conditions, approximate frequency and duration of tasks;
- What Risk Management Measures are in place e.g. gloves, goggles, etc.

1. Measured data

Workplace exposure data has a central role in exposure estimation. Extensive guidance is available on how exposure monitoring strategies can be implemented to evaluate the effectiveness of risk management advice. Exposure monitoring is not normally necessary, but the process needs to take into account the available exposure data from actual, analogous and modeled sources. In case no measured data for the chemical is available it is also possible to use appropriate analogous/surrogate data such as:

- other substances having similar exposure characteristics⁶ (e.g. volatility, dustiness), or
- other comparable activities considered likely to provide a reliable estimate of exposure for the scenario in question.

2. Predictive Estimation Models

Many exposure estimation models exist. They vary in complexity and purpose. Standard modeling approaches can be used to derive exposure estimates which describe the actual exposure situation. As assumptions and boundary conditions may vary between models, it is wise to document the assessment process in order to allow comparison between potentially deviating results for the same chemical. Examples of exposure estimation models are provided on page 106 of the Supplement.

The preferred tool (ECETOC TRA) is described in the supplement from page 109. A template with drop down menus for collection of Tier 1 information for ECETOC TRA can be downloaded from Cefic website:

<http://cefic.org/templates/shwPublications.asp?HID=750&T=806&P=2>

SECTION TWO IMPLEMENTATION

STEP 6: ASSESS EXPOSURE

Consumer Exposure

1. Identify relevant uses (e.g. AC, PC including subcategories)
2. Compile all available exposure data e.g. use level surveys
3. For AP, PC with no exposure data available calculate via tier 1 ECETOC TRA (consider duration of activity, ventilation, PPE, etc)
4. If calculation of DNEL / Exposure ratios indicated risk (Step 7 RCR >1), obtain more information if possible and assess with tier 2 tools (e.g. ConsExpo, REACT)

A consumer product is a product that can be purchased from retail outlets by members of the general public. Therefore, the general public may be exposed to substances inside consumer products. This includes exposure e.g. via solvents from the use of glues/adhesives, textile finishing chemicals or dyes in clothes; cleaning and household products or others.

Understanding the potential for consumer exposure is important because once released, possible means of exposure control (RMMs) beyond the point of sale are extremely limited and monitoring is difficult. Effective consumer RMMs are usually product-integrated measures (e.g. concentration limits, package size). Where RMMs take the form of consumer instructions, their efficiency is difficult to evaluate quantitatively. In general, consumer instructions are not very effective, unless consumer behavioral data provides evidence that a sufficient degree of implementation can be assumed.

Estimation of consumer exposure should include the following:

- Intended uses of the product or chemical substance. However, since consumers may not accurately follow instructions for use of products, a separate estimation of other reasonably foreseeable uses is recommended. In case the substance is used in several consumer products, a mapping of uses can be helpful.
- Exposure can occur via three exposure routes: inhalation, dermal contact and oral intake. Each exposure route must be calculated separately by using either measured data or predictive estimation models.

- Data availability. For consumers, exposure information often relies on modeled exposure estimates, based on article specifications (e.g. the content of the chemical in the article) as well as intended or foreseeable use.
- Careful consideration must be given to consumer subpopulations with particular exposure patterns (e.g. children), and this should be reflected in the risk assessment.

1. Measured data

In general measured data are preferred over modeled data but for most consumer exposure scenarios, measurements of actual consumer exposures are not be available. However, it may be possible that for one or more of the parameters used in the estimations, measurements are available and can be used to override the default values e.g. for room volumes, air exchange rates, migration rates, ad- and desorption as well as absorption rates (e.g. skin permeation rates). Biomonitoring programs are occasionally performed to study exposure to chemicals and the results may be valuable for exposure estimations. Furthermore, industry monitoring programs, particularly for occupational exposure, may be useful for comparative evaluations with consumer exposure. Therefore, the available measured data should be evaluated by expert judgment. Measured data from surrogate substances or analogues may also be useful when estimating exposure levels. Exposure estimations based on extrapolations using surrogate substances as well as surrogate scenarios (e.g. chamber measurements) should be transparent and well documented.

2. Predictive Estimation Models

Exposure estimation for consumers is often difficult due to limited data availability. As a result, consumer exposure information often relies on modeled exposure estimates, based on article specifications (e.g. the content of the chemical in the article) as well as intended or foreseeable use. Examples of exposure estimation models are provided on page 106 in the Supplement.

The preferred tool (ECETOC TRA) is described in the Supplement from page 109 in the Supplement. A template with drop down menus for collection of Tier 1 information for ECETOC TRA can be downloaded from Cefic website:

<http://cefic.org/templates/shwPublications.asp?HID=750&T=806&P=2>

SECTION TWO IMPLEMENTATION

STEP 6: ASSESS EXPOSURE

Environmental Exposure Assessment

1. Identify relevant uses (ERCs)
2. Compile all available exposure and emission data, e.g. environmental level surveys and physicochemical properties
3. Estimate exposures via calculation tools (e.g. ECETOC TRA)
4. Calculation of PEC/PNEC-ratios (Step 7)

Environmental exposure estimation is very complex and needs expertise to come to solid conclusions, it should include local and regional effects as well as inland and marine risks. Similar to the human health assessment it can be based on measured or modeled data and adequate assessment factors are used to compensate for uncertainties.

To ensure predicted environmental concentrations are realistic, all available exposure-related information on the substance should be used. The exposure assessment is more realistic when detailed information on use patterns is available (release into the environment; elimination; downstream uses of the substance).

Environmental Exposure assessment addresses all the following targets:

- Fresh and marine surface water (including sediment)
- Terrestrial ecosystem
- Top predators via the food chain (secondary poisoning)
- Micro-organisms in sewage treatment systems
- Atmosphere – mainly considered for chemical with a potential for ozone depletion, global warming, ozone formation in the troposphere, acidification
- Man indirect, i.e. man exposed via the environment

For environmental risk assessment derived exposure estimates (PECs) are compared to the predicted no-effect concentrations (PNECs) at each iteration. The following steps are included in the assessment of the releases of a substance to the environment and the resulting PECs for the relevant environmental compartments (air, water, sediment, soil):

- Select an appropriate method for release estimation
- Compile the relevant substance properties e.g. vapour pressure, water solubility and boiling point, molecular weight, octanol-water partition coefficient, melting point and information on ready biodegradability.
- Determine the quantity of the substance which is applied in a process
- Carry out manual or IT-based calculations to determine the releases at local and regional level based on generic emission equations.
- Apply the relevant emission rates in the selected tool, calculate the environmental distribution and derive the PECs.

The information that needs to be considered for the release estimation is:

- Tonnage
- Type of use for each Life Cycle Stage
- Type of use in the life cycle stage
- Distribution of production volume in the market
- Emission Pattern – Distribution in time and space
- Emission Pathways (Air, Soil, Water)
- Multiple emissions
- Emission factors
- Risks management measures to reduce emissions

SECTION TWO IMPLEMENTATION

STEP 6: ASSESS EXPOSURE

Tools to Calculate Exposure

The preferred tool (ECETOC TRA) is described from page 78 in Supplement. A template with drop down menus for collection of Tier 1 information for Ecetoc TRA can be downloaded from Cefic website:

<http://cefic.org/templates/shwPublications.asp?HID=750&T=806&P=2>

For the ECETOC TRA environmental part the release estimation is done for different supply chains using the conservative standards defined in the Environmental Release Classes from the use descriptor system. These release factors are very conservative and may lead to unacceptable exposures. Different industry sectors have developed (conservative) release factors that are typical for their sectors: Specific Environmental Release Classes (SPERCs).

These SPERCs now also included in the ECETOC TRA as drop down options. An overview of the SPERCs, with their release factor can be downloaded from Cefic website:

<http://cefic.org/templates/shwPublications.asp?HID=750&T=806>

In addition, for PEC exposure calculations on some of the above targets, the EUSES modeling programs (<http://ecb.jrc.ec.europa.eu/euses/>) and [EU-TGD-Spreadsheets](http://www.cem-nl.eu/eutgd.html) (<http://www.cem-nl.eu/eutgd.html>) can be used. EUSES is the software provided by the EU-commission. The EUTGD-Spreadsheet is an Excel-implementation provided by CEFIC. As these are European models, a number of parameters reflect the European Continent and therefore may not apply to other regions. If the chemical is used similarly to a pesticide, e.g. as a fertilizer in agriculture, consider models and use-scenarios used in pesticide risk assessment. Both, EUSES and the EU-TGD allow assessments to be performed with the limited information of the GPS Base Set. Under the US EPA Sustainable Futures Initiative (SF) a variety of computer-based models are available for environmental exposure estimation (<http://www.epa.gov/oppt/sf/>)⁴³.

Use Descriptors under REACH

To structure the large number of different uses of substances and preparations present in the different industry sectors ECHA has developed a system to describe uses in a standard and structured way. This so called “Use Descriptor System” is based on five separate categories. Each category has pre-defined descriptors which in combination with each other form a brief description of use. Use descriptors used in the chemical safety assessment (CSA) guidance of the ECHA are as follows:

- Sector of Use (SU)
- Product Category (PC)
- Article Category (AC)
- Process Category (PROC)
- Environmental Release Category (ERC)

- **Sector of Use [SU]**
In a supply chain a substance passes different industry and trade sectors before it reaches its final destination. Often the life cycle includes one or more formulation stages in the chemical industry, and one or more distribution stages in the trade sector. ECHA determined five main user groups which play a role along the life cycle of a substance: manufacturers of chemical substances (i.e. transforming substances into other substances) [SU8/9], companies (formulators) that mix and blend chemicals (without transforming into other substance) [SU10], industrial end-users that use the chemical in their manufacturing processes [SU3], professional end-users [SU22] and private households [SU21] that apply substances or preparations.
- **Chemical Product Category [PC]**
The Chemical Product Category characterizes the use of a substance by the type of end-use preparation (e.g. lubricant, cleaner, adhesive) in which the substance is known to be used. This is based on the consideration that the use of a preparation is closely related to exposure potential.

- **Process Category [PROC]**

Process category groups the way a substance is used or converted into a subsequent product (preparation or article). Application techniques or process types have a direct impact on the exposure to be expected and hence on the risk management measures needed.

- **Article Categories [AC]**

For dangerous substances processed into articles, the manufacturer or importer of the substance may find it necessary to specify which types of articles are covered in the CSA and the ESs. It will, for example, make a difference in terms of exposure whether a substance is used in textile-finishing of clothes (dermal contact, frequent washing) or as a component in insulation sheets for construction purposes.

- **Environmental Release Categories [ERC]**

Release estimation is the process whereby releases to the environment are quantified during the life cycle stages of a chemical, taking into account the different types of uses during these life cycle stages, the different emission pathways and receiving environmental compartments and the spatial scale of the emissions. To streamline the release estimation and make it accessible for data collection in the supply chain, environmental release categories (ERCs) have been developed. ERCs label the characteristics of a use based on different aspects relevant from environmental perspective.

How to apply REACH Use Descriptors: Choose one of the Sector of Use. In the next step the manufacturer, the formulator and the industrial end-user have to choose each one Process Category and one ERC. In order to cover uses for the consumer end-user, the professional user assigns a process category and an ERC. It is important to understand that for each applicant in the same supply chain there are several sets of uses which have to be completed.

Table 12: Exposure Estimation Models for Workplace

| Route of Exposure (Worker) | Exposure estimation models (for web link see glossary) |
|----------------------------|---|
| Inhalation | Ecetoc TRA www.ecetoc.org/tra Stoffenmanager www.stoffenmanager.nl COSHH tool www.coshh-essentials.org.uk EASE www.hse.gov.uk/index.htm ART www.advancedreachtool.com |
| Dermal | ECETOC TRA RISKOFDERM Dermal model (higher tool) EASE (Estimation and Assessment of Chemical Exposure) |
| Oral | Currently no methodologies or tools available |

Table 13: Exposure Estimation Models for Consumer

| Route of Exposure | Source of consumer exposure | Exposure estimation models (for web link see glossary) |
|-------------------|--|---|
| Inhalation | Chemical is released as a gas, vapor or airborne particulate. | ECETOC TRA ConsExpo 4.1 EUSES |
| Dermal | The chemical is contained in a preparation. This option is e.g., applicable when hands are put into a solution containing the chemical under evaluation. Chemical migrating from an article; applicable for example when residual dyes in clothing are in contact with skin and migrate from the clothing. | ECETOC TRA ConsExpo 4.1 EUSES |
| Oral | Chemical in a product unintentionally swallowed during normal use Chemical migrating from an article; applicable for example when a chemical migrates from a pen or textile. | ECETOC TRA ConsExpo 4.1 EUSES |

Table 14: Environmental Release Estimation Models

| Environmental Release Estimation Models (for web link see glossary) |
|---|
| <p>EUSES http://ecb.jrc.it/euses</p> <p>EU TGD http://ecb.jrc.ec.europa.eu/tgd/</p> <p>Higher Tier models have been developed Overview from: http://focus.jrc.ec.europa.eu</p> |

Table 15: Tools for Exposure Estimation

| Tool | Description / Source |
|---|--|
| Chemical Safety Assessment and Reporting Tool (Chesar) | The European Chemicals Agency has developed and Chemicals Exposure and Safety Assessment Reporting tool (CHESAR) for REACH. The Chesar tool uses the ECETOC TRA as the default exposure tool, but the results of other estimating tools or measured data can be used as well. The tool will be further developed over the next years and it can be downloaded from the IUCLID download website: http://echa.europa.eu/reach/software/iuclid5_en.asp |
| Downstream Users Organisation DUCC UserR | http://cefic.org/templates/shwPublications.asp?HID=750&T=806 |
| ECETOC TRA | See chapter below |
| Emission scenario documents published by OECD | www.oecd.org/document/46/0,3343,en_2649_34373_2412462_1_1_1_1,00.html |
| EMKG-EXPO-TOOL | The EMKG-EXPO-TOOL is part of the “Easy-to-use workplace control scheme for hazardous substances” of the Federal Institute for Occupational Safety and Health (BAuA). Within the context of REACH the BAuA-Unit 4.1 – Occupational Exposure – offers an IT-tool free of charge for a first exposure estimate at the workplace. This Tier 1 assessment is only valid for inhalation exposure. www.reach-clp-helpdesk.de/reach/en/Exposure/Exposure.html |
| Generic Exposure Scenarios (GES) | GES describe exposure assessments for (groups of) substances for an area of operation within industry including Risk Management Measures & Operational Conditions relevant for safe use of a group of substances with a similar risk profile http://cefic.org/en/reach-for-industries-libraries.html |
| Sector groups use descriptors | This gives overview of links to different sectors with their use mappings http://cefic.org/en/reach-for-industries-libraries.html |
| Specific Environmental Release Classes (SPERCs) | Describe the typical operations in their sectors including (conservative) release factors and efficiencies of RMM/OC. http://cefic.org/templates/shwPublications.asp?HID=750&T=806 |

ECETOC Targeted Risk Assessment Tool

Targeted Risk Assessment (ECETOC TRA), an assessment tool developed by the European Centre for Ecotoxicology and Toxicology for Chemicals (ECETOC). ECETOC-TRA is a comprehensive risk assessment tool incorporating the concept of a substance's life cycle, and it enables a simultaneous assessment of occupational, consumer, and environmental exposure, and offers risk characterization functions. The TRA assessment tools are made available as two individual assessment tools for worker or consumer assessment. Alternatively, the two tools, completed by the environmental tool, are provided in an integrated version which allows the user to perform the assessments via one interface. It uses PROC, PC and AC, and ERC for input data to estimate occupational exposure, consumer exposure, and environmental exposure, respectively. The ECETOC TRA⁴⁴ (<http://www.ecetoc.org/tra>) can be downloaded free of charge and requires the following parameters as hazard reference values:

- Worker risk assessment: reference values for worker inhalation exposure and dermal exposure;
- Consumer risk assessment: reference values for consumer inhalation exposure, dermal exposure, oral exposure, and the worst case scenario for consumers;
- Environmental risk assessment: reference values for wastewater plant micro-organisms, freshwater organisms, marine organisms, freshwater sediment organisms, marine sediment organisms, soil compartment organisms, and human exposure via the environment. All the reference values are required for environmental risk assessment.

The ECETOC TRA model for workers considers 15 broadly applicable scenarios, which are to cover the vast majority of uses of chemicals. These scenarios include for instance use in a closed batch process i.e. where only limited opportunity for breaching arises e.g. 'sampling' or 'Roller application or brushing of adhesives and other surface coatings'. For each scenario, the TRA produces a banded exposure prediction for an 8 hour work day. The TRA exposure prediction is based on measured workplace data. The input variables are chemical vapor pressure (in volatility bands) or dustiness, level of risk management (with or without local exhaust ventilation), and exposure duration bands. The 15 broad ECETOC scenarios match well with the process categories outlined in the REACH Use Descriptor System.

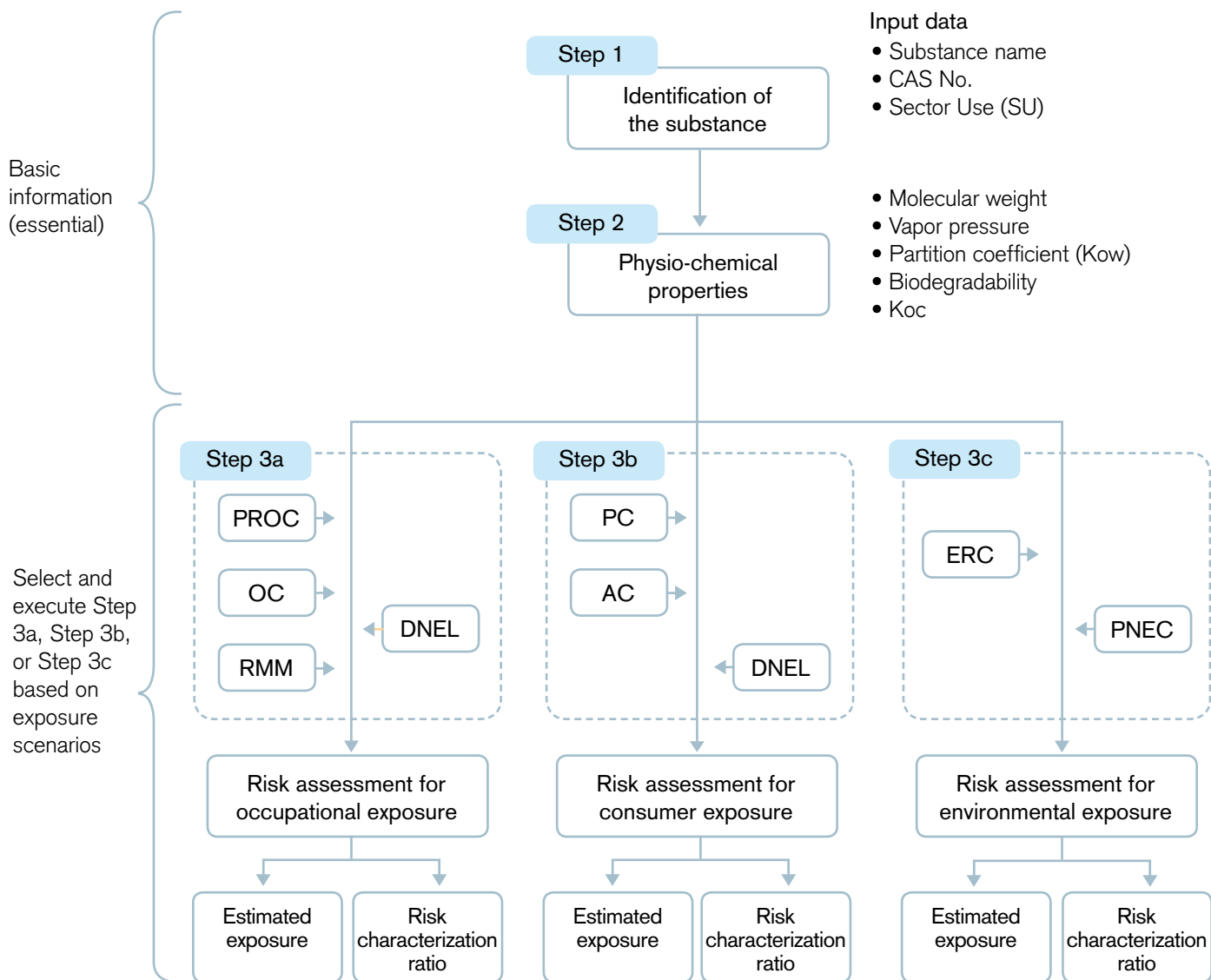
The ECETOC TRA model for consumers applies the algorithms of the EU Technical Guidance Document on risk assessment of chemicals for calculating exposure resulting from exposure of consumers to different broad product types. These product types include for instance 'adhesives, sealants', 'paints', or 'washing and cleaning products'. For each product type contained in the set of the ECETOC TRA, a set of default product use parameters has been defined as input for the exposure assessment algorithms. The 19 ECETOC product classes match well with the product categories outlined in the REACH Use Descriptor System.

When using ECETOC-TRA, a user inputs data in an Excel worksheet with embedded macros (in Steps 1 to 3). Steps 1 and 2 provide essential information, and selective information is obtained in Step 3.

1. Input of substance-specific information
2. Input of physico-chemical properties
3. Input of exposure and hazard information necessary for assessing the risk for the exposure target (workers, consumers, the environment)

ECETOC-TRA outputs an estimated exposure (EE) and risk characterization ratio (RCR) based on input data. The color of the RCR column turns green when the risk is under control ($RCR < 1$) or turns pink when the risk is not properly controlled ($RCR > 1$) based on the result of the risk characterization. For more information see Annex.

Figure 5: Workflow of ECETOC TRA



Examples of Exposure Derivation using ECETOC

Input data

- Identity: Process substance
- Volatility Low volatility material
- Dustiness: Not dusty

Process category selection

In the web tool this is done simply by selecting the “process category, in ECETOC TRA called: generic exposure scenario” and identifying the duration of the activity and whether Local Exhaust Ventilation is present.

Category A

- In a closed process with no likelihood of exposure
- Use of the substances in a high integrity contained system where little potential for exposures exists, e.g. any sampling is via closed loop systems
- Duration of Activities – More than 4 hours per day Duration
- Local Exhaust Ventilation

Estimated exposure values

- Inhalation Exposure Value = **0.01 ppm**
- Dermal Exposure Value **Dermal exposure unlikely**

Category B

- Roller application or brushing of adhesives and other surface coatings
- Application of adhesives and similar coatings using low energy sources e.g. brush or rollers.
- Also applies to printing activities.
- Duration of Activities – 1 to 4 hours per day
- No Local Exhaust Ventilation

Estimated exposure values

| Inhalation exposure | = 100 ppm for 8 hours duration for a low volatility material) |
|---|---|
| Exposure modifying factor (Actual duration is 1-4 hours) | 0.6 |
| Estimated exposure | 100 ppm x 0.6 = 60 ppm |
| Estimated dermal exposure | Exposure Scenario surface area = 960 cm ² = 960 mg Predicted EASE dermal exposure 1000 µg/cm ² /day The exposure (for a 70 kg worker) = 960 cm ² x 1000 µg/cm ² /day / 70 kg = 13.71 mg/kg/day |

Consumer exposure example

- Dermal exposure to a substance in a solution.
- The identified use is “Washing and cleaning products”
- The concentration of the substance to be assessed for dermal exposure in the undiluted product is 5%, in the diluted product; the concentration is 0.25% due to a 1:20 dilution with water.
- The area of contact to skin is 840 cm² and a layer thickness THder of 0.01 cm (Vder=8.4 cm³).
- According to the equation given under ‘Dermal A’ the concentration on skin, the dermal dose Dder= 0.025 mg/cm²
- The external dose per body weight is 0.35 mg/kg BW assuming a body weight of 60 kg.
- RMMs are not considered in the quantitative exposure estimation because consumer compliance to the advice ‘wear gloves while cleaning’ cannot be ascertained. However, it is considered good advice if this was added as a labelling instruction for consumer use.

SECTION TWO IMPLEMENTATION

STEP 7: CONDUCT RISK CHARACTERIZATION

A very important concept is the distinction between hazard and risk.

Hazard defines the inherent property of a chemical agent having the potential to cause adverse effects when an organism, system or population is exposed to that agent. You performed the hazard characterisation in Step 5.

Risk establishes the probability of the adverse effect in an organism, system or population to occur under specified circumstances.

“Risk is the possibility of suffering harm from a hazard”

Risk Characterization is the final step in the risk assessment process: it combines the results of both the hazard characterization and the exposure assessment in order to estimate the nature and magnitude of a potential risk from a chemical substance. Risk assessment is the subsequent evaluation of the risk characterization and includes the recommendation of additional risk management practices if the outcome of the characterization indicated them as appropriate.

Risk Characterization examines particular endpoints and assesses whether the risk related to each endpoint is at an acceptable level. For example, short-term estimated exposures should be compared to short-term hazard toxicity endpoints, while repeated daily estimated exposures should be compared to chronic hazard toxicity endpoints. When suitable predicted no-effect concentrations (PNEC), No observed adverse effect levels (NOAEL) or derived no-effect levels (DNELs) are available, a decision can be derived if risks are adequately controlled. When these quantitative no-effect levels cannot be established for certain effects, a qualitative assessment of the risk shall be carried out.

NOTE: It might be necessary to develop additional information in order to conduct a reliable risk characterization. The decision of whether and how much additional information is required depends upon case-by-case analysis. For example, if a substance used in children's toys is known to be directly associated with exposure to the children who play with the toys, then the exposure assessment should include relevant exposure scenarios.

How to Conduct the Risk Characterization

1. Check if estimated exposure (outcome step 6) is below hazard threshold dose (outcome step 5)
2. If not refine assessment and / or implement additional risk management measures
3. If yes, communicate safe conditions of use (step 8)

Risk Characterisation Approaches

As mentioned under step 5, there are different approaches to risk assessment but the basic principles of methodology remain the same. The classical approach is the derivation of a MOS (Margin of Safety) also termed Margin of Exposure (MOE). Under REACH, however, the Risk Characterization Ratio (RCR) is calculated, where the exposure levels are compared to suitable no-effect levels for the relevant time and spatial scales for each of the protection targets: occupational, consumer and environment (e.g. ratio of PEC to PNEC or Exposure/DNEL). Both methods use dose descriptors such as the NOAEL (NO Adverse Effect Level) and Assessment (Uncertainty) Factors and should come to the same conclusion on the same data set; however, the way of presenting the outcome is different.

An advantage of the DNEL approach is that the DNEL is directly comparable to exposure estimates and measurements, and any new exposures can therefore easily be compared with the available DNEL. In the result of the DNEL derivation relevant assessment factors are already accounted for – in case of the MOS / MOE they have to be considered after deriving the result.

NOTE: Occupational Exposure Limits can be used as Reference Value instead of DNEL for DNEL for the acute toxicity.

SECTION TWO IMPLEMENTATION

STEP 7: CONDUCT RISK CHARACTERIZATION

Risk Characterisation Ratio (RCR) calculation as in REACH

Derive Human Health RCR by dividing Exposure with DNEL: In case the leading health effect is a threshold effect with a DNEL, the quantitative risk characterisation is as follows:

$$\text{RCR} = \text{EXPOSURE} / \text{DNEL}$$

If Exposure < DNEL → Risk is adequately controlled

If Exposure > DNEL → Risk is NOT adequately controlled

RCR ≥ 1: **Risk is high:** detailed assessment and risk reduction measures required

RCR < 1: **Risk is controlled:** No further action required

For a worked through example refer to page 124.

For human health end-points, a distinction must be made between effects exerted by a threshold and non-threshold mode of action:

- For threshold effects where a DNEL can be set, the RCR is the ratio of the estimated exposure and the DNEL.
- For non-threshold effects (e.g. non-threshold mutagens and non-threshold carcinogens) a no-effect level, and thus a DNEL, cannot be established. However, it may be possible, if data allow, to set a DMEL (derived minimal effect level), a reference risk level considered to be of very low concern. Risk characterization then entails a comparison between the estimated exposure and the DMEL, but it should be recalled that the resulting “RCR” is not related to a no-effect level.

$$\text{RCR} = \text{EXPOSURE} / \text{DMEL}$$

If Exposure < DMEL → Exposure is controlled to a risk level of low concern

If Exposure > DMEL → Risk is NOT controlled

RCR ≥ 1: **Risk is high:** detailed assessment and risk reduction measures required

RCR < 1: **Risk is controlled:** No further action required

Derive Environmental RCR by dividing PEC with PNEC

Instead of deriving a DNEL, as for the human health hazard characterisation – an environmental risk characterisation ratio (RCR) is calculated using the formula below, where the PEC is the Predicted Environmental Concentration and PNEC is the Predicted No Effect Concentration.

$$\text{RCR} = \text{PEC} / \text{PNEC}$$

Risk is under control when RCR is smaller than 1 – i.e. when the PEC is smaller than the PNEC:

RCR ≥ 1: **Risk is high:** detailed assessment and risk reduction measures required

RCR < 1: **Risk is controlled:** No further action required

SECTION TWO IMPLEMENTATION

STEP 7: CONDUCT RISK CHARACTERIZATION

Margin of Safety (MOS) or Margin of Exposure (MOE) calculation

The difference between the level of exposure and the NOAEL is a first indication of the risk and the resulting ratio is called Margin of Exposure also termed Margin of Safety (MOS). For effects for which an N(L)OAEI, can be identified, risk characterization is carried out by quantitatively comparing the outcome of the effects assessment to the outcome of the exposure assessment. This is to be done for all relevant combinations of exposed human (sub) populations and toxicological endpoints. For this step, the magnitude by which the N(L)OAEI exceeds the estimated exposure needs to be considered taking account of the following parameters:

- the uncertainty arising, among other factors, from the variability in the experimental data;
- and intra- and interspecies variation;
- the nature and severity of the effect;
- the human population to which the quantitative and/or qualitative information on exposure applies;
- the differences in exposure (route, duration, frequency and pattern);
- the dose-response relationship observed;
- the overall confidence in the quality of the data.

Expert judgment is required to weigh these individual parameters on a case-by-case basis. The approach used should be transparent and a justification should be provided for the conclusion reached. In very clear-cut cases, conclusions can be reached at an early point in the procedure, whereas border-line cases require further analysis of the effects and exposure data available and may result in a request for further information. MOS is the ratio of the outcomes of the effects and exposure assessment and is derived in the following way:

$$\frac{\text{N(L)OAEI (mg/kg bw/day)}}{\text{Exposure (mg/kg bw/day)}} \quad \text{or} \quad \frac{\text{N(L)OAEI (mg/m}^3\text{)}}{\text{Exposure (mg/m}^3\text{)}} = \text{MOS / MOE}$$

If MOS (or MOE) > 100 no concerns

If MOS (or MOE) < 100 cause for concern, refine analysis or control exposures

If MOS (or MOE) ~ 1, refine analysis or control exposures

If MOS (or MOE) < 1, cause for high concern, direct measures needed

See page 125 for a worked through MOS example, and page 127 for MOE.

DNEL versus Margin of Safety

$$\text{MOS} = \frac{\text{NOAEL OR NOAEC}}{\text{Exposure}}$$

If MOS > Overall Assessment Factor → No concern

If MOS < Overall Assessment Factor → Concern

$$\text{DNEL} = \frac{\text{NOAEL or NOAEC}}{\text{Overall Assessment Factor}}$$

If Exposure < DNEL → Risk is adequately controlled

If Exposure > DNEL → Risk is NOT adequately controlled

Conclusions from the Risk Characterization

Possible conclusions of the risk characterization:

- There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already. The substance is of no immediate concern and need not be considered again until further information become available.
- The substance is of concern and further information is required for revision of the assessment. Steps 5 and 6 may need to be repeated to obtain more detailed information on effects and exposure specific to the chemical and its uses. The risk characterization is then performed again.
- The substance is of high concern, further information should be gathered immediately and/or recommendations for risk reduction should be implemented immediately. Once RMM are in place, the risk should be characterized again to see if the RMM are effective in reducing concern.

SECTION TWO IMPLEMENTATION

STEP 7: CONDUCT RISK CHARACTERIZATION

Adequate control of risk for a substance is demonstrated when the outcome of both the hazard assessment and exposure assessment are robust and where either RCRs for all exposures (for all compartments, routes, populations and durations) related to all exposure scenarios and all end-points are below one; or the respective Margin of Exposure / Margin of Safety is >100 .

More than one conclusion may be reached for a particular chemical in relation a) different properties of the chemical or b) different uses of the chemical and/or the different human populations involved. As a very simple example, risk reduction may be indicated at the workplace but not for the general population. More complex situations might need an evaluation on a case by case basis. If for example, a chemical which is only used at workplaces is already identified as being a (genotoxic) carcinogen - workplace exposure should automatically be reduced to the lowest possible level. Any use of such chemicals in end consumer products would need careful consideration and significant risk management precautions.

The outcome of the risk characterization may be that no further information/testing or risk reduction measures are required. If this is not the case, and the risk reduction measures already being applied are not sufficient, then additional risk management measures are needed. For your company internal documentation you should always provide justification for the conclusions reached. Ideally qualitative and quantitative aspects should be combined to create a comprehensive report addressing whether there are reasons for concern and why.

Risk Management Measures (RMMs)

If the risk assessment outcome indicates the chemical is toxic (or capable of becoming toxic) at expected human or environmental exposure levels, then risk management measures (RMMs) must be applied. RMMs reduce chemical emission and exposure, thereby reducing risk. RMMs should be proportionate with the characterized risk. See the following links for more information on RMM:

- ECHA Guidance on information requirements and chemical safety assessment⁴⁵ (http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_part_d_en.pdf)
- CEFIC library for RMMs⁴⁶ www.cefic.org/files/downloads/RMM%20Library%20.xls

If RMMs are already in place, they should be evaluated to ensure they are adequate to protect human health and the environment. Additional risk management measures may need to be considered and implemented. Where information is insufficient to complete a risk characterization, then additional information on hazard and exposure must be gathered in order to conduct detailed risk assessments. This should prioritize high-risk products or uses.

This process of evaluation – information-gathering – risk assessment must be repeated until a meaningful risk characterization of the target substances is feasible. It is important to explore and re-examine all available data in order to avoid redundant effort or unnecessary animal testing. RMMs include but are not limited the following:

- **Risk Communication**
Making information available about chemical risks and risk management measures to suppliers, customers is an important element of product stewardship. Effective risk communication provides the necessary information for safe chemical handling and environmental protection. There are a variety of risk communication mechanisms available, such as Material Safety Data Sheets and product labels, training and education...
- **Occupational hygiene measurements and biomonitoring**
Measure the exposure at the workplace. Include more work sites to find out the highest exposures and to focus the risk management measures/controls. For the carcinogenic and reprotoxic compounds it may be justified that occupational health care follows the exposure e.g. by biomonitoring.

SECTION TWO IMPLEMENTATION

STEP 7: CONDUCT RISK CHARACTERIZATION

- **Training**

Training may include e.g. the hazardous properties of the chemicals, safe handling of the chemicals, maintenance and storage of the personal protective equipment (PEE), use and maintenance of the local ventilation, how to act in the case of accident.

- **Preparing the safety instructions**

The producer or importer may have – and by the implementation of the REACH they will have – provided instructions for the safe use of the chemical. More specific instruction, where the conditions and processes of a particular plant are considered, may be useful.

- **Substitution**

In certain cases it may be possible feasible to substitute a dangerous chemical with a safer different chemical or with a safer process in an effort to reduce risk. However, Substitution does not necessarily guarantee a reduction in overall risk, it is therefore critical that any substitute material and processes be thoroughly evaluated and tested in order to avoid an inadvertently increased risk to human health and/or the environment.

- **Public Concern Evaluation**

In addition to risk management measures, if there is public concern about particular chemicals, a communication strategy may need to be developed or modified to address perceived risk. In some cases, public concern can be a significant driver, and a company may wish to expand its risk communication for certain chemicals beyond the scientific assessments of exposure and hazard that are typically used to characterize risk. The approaches to considering public concern will vary according to the customs, laws and practices in a region.

- **Making Relevant Product Stewardship Information Available to the Public**

Increased transparency regarding chemicals and other relevant product stewardship information helps build credibility for the company's product stewardship program. It further helps build trust for the entire chemical industry by clearly demonstrating to all that the industry is knowledgeable about its chemicals and their related risks and implements appropriate risk management measures. With this in mind, an essential element of the Global Product Strategy is that companies will make relevant product stewardship information available to the public.

- **Internal Monitoring**

Monitoring should provide evidence that the management system requirements are being met, and provide the basis for defining any action needed to improve product stewardship performance. Of central importance is assessing the degree to which the company and business policies, objectives and product stewardship performance targets are being supported by effective product stewardship systems and programs. Chemical risk characterization and related product stewardship communication and risk management efforts are important starting points for determining what activities are priorities to cover in a product stewardship monitoring program.

- **Auditing**

Conducting audits is another method for identifying areas for improvement in the product stewardship management system. Individuals conducting the audit should be experienced in product stewardship practices and systems. If they are considered “independent” from the area being audited, that can improve the rigor of the audit outcomes. Audit results should be communicated in such a way that the parties responsible can take appropriate corrective action. Providing audit results and reports of subsequent actions taken to company management can improve audit effectiveness.

- **Minimizing the time of the exposure**

Optimize operational conditions so that workers spend less time in contact with the chemical.

- **Decreasing the amount of chemical used**

Optimize efficiency of the product, so that you can use less of the substance of concern e.g. limiting concentration of chemical in preparation.

- **Limiting package size** in order to minimize potential exposure of end consumers.

NOTE: Standard phrases for communicating RMMs have developed and agreed in industry to facilitate harmonized communication. This standard phrase library is managed by BDI and called European Phrases Catalogue. These phrases are freely available in English and German and can be downloaded from the BDI⁴⁷ website: <http://reach.bdi.info/378.htm>

Calculation of RCR (Risk Characterization Ratio)

a) Worker

- Long-term inhalation

$$\frac{\text{Exposure}}{\text{DNEL}} = \frac{938 \text{ mg/m}^3}{100 \text{ mg/m}^3} = \text{RCR } 9.4$$

RCR \geq 1: Risk is high: detailed assessment and risk reduction measures required

- Long term dermal exposure systemic

$$\frac{\text{Exposure}}{\text{DNEL}} = \frac{42.86 \text{ mg/kg bw}}{143 \text{ mg/m}^3} = \text{RCR } 0.3$$

RCR < 1: Risk is controlled: No further action required

b) Environment

- Aquatic

$$\frac{\text{PEC}}{\text{PNEC}} = \frac{8 \text{ mg/l}}{125 \text{ mg/l}} = \text{RCR } 0.06$$

RCR < 1: Risk is controlled: No further action required

Calculation of the MOS (Margin of Safety)

a) Worker

The total daily body burden resulting from dermal and inhalation exposure would be $0.03 + 0.04 = 0.07$ mg/kg/day (approximate mean value). This value is approximately 7 times lower than the NOAEL of 0.5 mg/kg/day for neuropathological effects and about 30 times lower than the LOAEL of 2 mg/kg/day for the slight neuropathological effects that were observed in an animal study.

| Effect | Estimated total exposure (mg/kg/day) | NOAEL | LOAEL | Estimated MOS based on NOAEL | Estimated MOS based on LOAEL |
|---------------|--------------------------------------|-------|-------|------------------------------|------------------------------|
| Neurotoxicity | 0.07 | 0.5 | 2 | 7 | 30 |
| Fertility | 0.07 | 5 | 12 | 70 | 170 |

Conclusion Worker

- For occupational exposure the potential for risk exists for neurotoxicity effects due to $MOE < 100$.
- Risk can not be adequately controlled, exposure needs to be minimized.

b) Consumer

The total daily body burden arising as a result of skin exposure for consumers is estimated to be $0.0007 + 5 \cdot 10^{-5} = 0.001$ mg/kg/day. The major contribution comes from dermal exposure via the use of cosmetics, based on a level of monomer in the polymer of 0.01%.

| Effect | Estimated total exposure (mg/kg/day) | NOAEL | LOAEL | Estimated MOS based on NOAEL | Estimated MOS based on LOAEL |
|---------------|--------------------------------------|-------|-------|------------------------------|------------------------------|
| Neurotoxicity | 0.001 | 0.5 | 2 | 500 | 2000 |
| Fertility | 0.001 | 5 | 12 | 5000 | 12000 |

Conclusion Consumer

- MOE > 100
- Risk adequately controlled, no further actions needed

Calculation of MOE (Margin of Exposure) for non-threshold cancer effect

| Type of Exposure | Effect | NOAEL (mg/kg-d) | Exposure Dose (mg/kg-d) <i>(Source of Value)</i> | Calculation | MOE | Potential for Risk? |
|---------------------|----------|-----------------|--|----------------------------------|------|---------------------|
| Worker | Dev. Tox | 10 | 0.599 <i>(ChemSTEER APDR, Inhalation)</i> | $\frac{10}{0.599}$ | 16.7 | Yes |
| General Pop. | Dev. Tox | 10 | 8.13x10⁻² <i>(E-FAST ADR_{pot}, Fish Ingestion)</i> | $\frac{10}{8.13 \times 10^{-2}}$ | 123 | Low |

Conclusion

- For occupational exposure the potential for risk exists for non-cancer effects due to MOE < 100
- Risk can not be adequately controlled, exposure needs to be minimized.

SECTION TWO IMPLEMENTATION

STEP 8: DOCUMENT OUTCOMES

Document the Risk Assessment Process and Outcome

Proper risk assessment includes, among others things, making sure that all relevant risks are taken into account (not only the immediate or obvious ones), checking the efficiency of the safety measures adopted, documenting the outcomes of the assessment and reviewing the assessment regularly to keep it updated.

As this documentation will contain data of proprietary nature it should stay company internal and does not have to be shared with co-producers or the public. In the next step we will develop a format that can be used to communicate the essential information in a transparent way with interested stakeholders (see GPS Safety Summary below).

The objective of documenting the outcomes of the risk assessment is to provide:

- Company-specific documentation of the process followed throughout the risk assessment. This is important because stakeholders might ask for justification for the conclusions of the risk assessment. Your company-internal protocol provides you with evidence you need in order to justify your conclusions.
- A description of risk management practices the company has implemented to minimize risks from these hazards and exposures.
- A clear and concise description of the chemical, its potential hazards and potential for human or environmental exposure.

Documentation should summarize the following:

- Criteria used for prioritization of the chemical
- Hazard information collected
- Outcome of the hazard characterization
- Exposure information collected
- Outcome of the exposure assessment
- Outcome of the final risk assessment (e.g. safe, not safe, further steps required, etc.)
- Risk management measures implemented or to be implemented down the supply chain

Besides this company internal documentation increased transparency regarding chemicals and other relevant product stewardship information helps build credibility for the company's product stewardship program. It further helps build trust for the entire chemical industry by clearly demonstrating to all that the industry is knowledgeable about its chemicals and their related risks and implements appropriate risk management measures.

With this in mind, an essential element of the Global Product Strategy is that companies will make relevant product stewardship information available to the public.

Prepare a GPS Safety Summary

The GPS Safety Summary for a chemical is the final step of the GPS risk assessment system. The GPS Safety Summary is not intended to provide an in-depth review of the risk characterization process or detailed health and safety information. Nor is it intended to replace required communication documents such as the Safety Data Sheet or REACH Chemical Safety Report – these documents should always and at any case be consulted before industrial use of the chemical.

Rather, the GPS Safety Summary is intended to provide the general public with a short overview of relevant information for the chemical (or categories of chemicals) addressed:

- **Target Audience:** General public, all interested stakeholders
- **Content:** GPS Safety Summary features straight-forward explanations of potential hazards and exposure scenarios, as well as use, safe handling, and risk management information. There is no global standard mandated format of a GPS Safety Summary; it is at the discretion of each company to define the content and layout.

The summary should be fairly basic and understood by a layman, therefore the use of chemical and/or toxicological terminology is minimized in favor of general classification terms. Use of analogies to commonly recognized products may be helpful. The specific content of the summary is not prescribed. The presentation of results should utilize the concept of “proportionate to risk” or the degree of potential public concern.

SECTION TWO IMPLEMENTATION

STEP 8: DOCUMENT OUTCOMES

For example:

- The uses and applications of the chemicals and associated benefits.
- The potential hazards of the chemical: chemicals associated with serious physical hazards or significant toxicity should be described in more depth than less hazardous chemicals.
- The potential for exposure of the chemical:
e.g. level of details highest for consumer product chemicals.

The format (e.g. simple paragraphs or questions and answers) can vary depending upon the amount of information to be presented. One option is to present the document as a part of the company's technical and marketing literature and therefore should be consistent with other company product literature.

Recommended elements of the GPS Safety Summary

The list below captures some of the elements that can be incorporated into the GPS Safety Summary. For a template refer to pages 132-135.

- Chemical identity (or category description)
- Uses - applications, functions
- Physical / chemical properties
- Health effects
- Environmental fate and potential effects
- Exposure - exposure potential
- Risk management - recommended measures
- First-aid measures
- Fire-fighting measures
- Accidental release measures
- Disposal consideration
- Handling and storage

Although recommended, there may be company-specific reasons for not including one or more of these elements. On the other hand, there are other elements that might strengthen a company's stewardship message, such as:

- Benefits of chemical
- Special considerations
- Production
- Findings by agencies / scientific organizations
- Regulatory compliance
- Sources for additional information
- Conclusion statement
- Contact information

Not all elements are appropriate for each summary, and the order in which they are presented is dependent upon the message to be conveyed. For example, if the chemical presents minimal hazards and little risk management action is appropriate, then the emphasis should be on the physical properties, health effects or environmental effects. Conversely, if the chemical does present potential risk, then the company risk management actions should be emphasized.

Around 1000 GPS safety Summaries available via the ACC webpage. ACC has created a portal to access the product stewardship summaries⁴⁸ currently available for each company on this page <http://reporting.responsiblecareus.com/Search/PSSummarySearch.aspx>

Generic Template GPS Safety Summary [PRODUCT NAME]

The summary should be fairly basic and understood by a layman.

1. General Statement

Summarize the uses and benefits of the product and why you believe it is safe.

2. Chemical identity

CAS

EINECS

Name

Structure

3. Uses and Benefits

4. Physical / chemical properties

Available from (M)SDS or other technical data sheets.

Focus on properties affecting exposure and environmental health.

5. Health Effects

Summarize conclusions on health effects based on the toxicity testing results or structural activity relationship based findings. List result of key studies important for conclusion.

6. Environmental Effects

Summarize conclusions on environmental effects e.g. aquatic and/or terrestrial toxicity, environmental fate, biodegradation. List result of key studies important for conclusion.

7. Exposure

Describe nature and level (expected concentration) of industrial, consumer and environmental use and describe practices that limit exposure.

8. Risk Management Recommendations

Describe practices for use and exposure at workplace, consumer and the environment. Exposure and Risk Management Recommendations can be combined into a “Potential Exposures” section with subheadings for Workers, Consumers, and Environment.

9. First-aid measures

10. Fire-fighting measures

11. Accidental release measures

12. Disposal consideration

13. Handling and storage

14. State Agency Review

List whether the chemical has been or is currently under review by a regulatory agency.

15. Classification and Labeling

State whether the chemical is already classified according to e.g. Annex 1, GHS, etc.

16. Conclusion

General Statement about risk of the chemical and rational.

17. Contact Information within company

18. Date

State the date of finalization of the Safety Summary.

GPS Safety Summary Elements

| | MSDS | OECD SIAR | HPV Challenge Work |
|---|------|-----------|--------------------|
| Recommended elements in GPS Safety Summary | | | |
| Chemical identity | | | |
| Uses – applications | | | |
| Uses – functions | | | |
| Physical – chemical properties | | | |
| Health effects | | | |
| Environmental effects | | | |
| Exposure potential | | | |
| Risk management measures | | | |
| Optional elements for GPS Safety Summary | | | |
| Exposure –production | | | |
| Special considerations | | | |
| Uses – benefits | | | |
| Product stewardship programs | | | |
| Findings by agencies | | | |
| Regulatory compliance | | | |
| Conclusion statement | | | |
| Contact information | | | |
| Date | | | |

GLOSSARY

DEFINITION OF TERMS USED IN THIS DOCUMENT

| Term | Definition |
|---|--|
| Adverse effect | Change in morphology, physiology, growth, development or lifespan of an organism which results in impairment of its functional capacity or impairment of its capacity to compensate for additional stress or increased susceptibility to the harmful effects of other environmental influences. |
| Assessment factor | <p>For human health, this is an uncertainty factors to estimate reference values based on the Point of departure such as no-observed-adverse-effect levels (NOAELs) or lowest observed adverse- effect levels (LOAELs) from studies in animals or from the human experience data. A value of 100 is normally used to derive an acceptable daily intake (ADI), a tolerable daily intake (TDI) or a reference dose (RfD) for the general population based on a NOAEL or LOAEL from a chronic study in animals. This value represents the product of two factors of 10, which allow for interspecies differences and human variability. Chemical specific adjustment factor to extrapolate for interspecies differences and human variability. For guidance⁴⁹ document see www.inchem.org/documents/harmproj/harmproj/harmproj2.pdf</p> <p>For environment, this is an uncertainty factors to estimate reference values based on the point of departure such as predicted-no-effect-concentration (PNEC) from studies in fish, crustacean, and/or algae or other aquatic plant and waste treatment plant. The factor is dependent on the number of pieces of the available data set. (REACH guidance document, IR-CSA guidance R10, 2008, Table R.10-4).</p> |
| Benchmark Dose (BMD) or Concentration (BMC) | <p>A dose or concentration that produces a predetermined change in response rate of an adverse effect (called the benchmark response or BMR) compared to background.</p> <p>Many computer software packages have been created specifically for modelling toxicology data and calculating benchmark doses and their confidence limits: BMDS: available for free download from the U.S. Environmental Protection Agency (www.epa.gov/ncea). And ToxTools: commercial software available from Cytel Software Corporation, Cambridge, MA (www.cytel.com).</p> |
| Chemical | A chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability or changing its composition. |

| Term | Definition |
|--|---|
| Chemical in commerce | Sold into a market |
| ConsExpo 4.1 | <p>To mathematically predict human exposure to consumer products RIVM has developed the software model ConsExpo. This program is designed for the use by expert exposure assessors only. To enhance transparency and standardization, for a number of product categories, default parameter values have been compiled in so-called fact sheets.</p> <p>www.rivm.nl/en/healthanddisease/productsafety/ConsExpo.jsp</p> |
| DEREK | <p>LHASA Limited has been developing knowledge-based expert systems for toxicity and metabolism prediction in collaboration with industry and regulatory authorities. These systems, DEREK, StAR and METEOR, use rules to describe the relationship between chemical structure and either toxicity in the case of DEREK and StAR, or metabolic fate in the case of METEOR.</p> <p>www.lhasalimited.org</p> |
| Downstream user | Any natural or legal person established in a country, other than the manufacturer or the importer, who uses a chemical, either on its own or in a preparation, in the course of his industrial or professional activities (a distributor or a consumer is not a downstream user). |
| EASE (Estimation and Assessment of Chemical Exposure) | <p>EASE is a general-purpose predictive model for workplace exposure assessments. It is an electronic, knowledge based, expert system which is used where measured exposure data are limited or not available. The model is in widespread use across the EU for the occupational exposure assessment of new and existing substances. EASE is essentially a series of decision trees.</p> <p>For any substance, the system asks a number of questions about the physical properties of the substance and the circumstances of its use. For most questions, the EASE user is given a multiple-choice list from which to select the most appropriate response. Once all the questions have been answered, the exposure prediction is determined absolutely by the choices made. EASE can be used to estimate inhalation and dermal exposure. The dermal model is less developed than the inhalation model, and its outputs should be regarded as no more than first approximation estimates.</p> |

GLOSSARY

DEFINITION OF TERMS USED IN THIS DOCUMENT

| Term | Definition |
|--|--|
| Easy-to-use Workplace Control Scheme for hazardous chemicals (COSHH- tool) | The Control of Substances Hazardous to Health Regulations is a United Kingdom Statutory Instrument that stipulates general requirements on employers to protect employees and other persons from the hazards of substances used at work by risk assessment, control of exposure, health surveillance and incident planning. COSHH Essentials provides advice on controlling the use of chemicals for a range of common tasks, e.g. mixing, or drying. www.coshh-essentials.org.uk |
| ECETOC TRA | The TRA assessment tools are made available as two individual assessment tools for worker or consumer assessment. Alternatively, the two tools, completed by the environmental tool, are provided in an integrated version which allows the user to perform the assessments via one interface. All ECETOC TRA tools can be downloaded free of charge. www.ecetoc.org/tra |
| ECVAM | European Centre for the Validation of Alternative Methods. http://ecvam.jrc.it/ |
| Environmental Release Category (ERC) | The 'Environmental Release Category' defines activities for which typical emissions into the environment can be assumed. The categories are codified by numbers with a preceding 'ERC' (Example: Production of plastics – ERCC6c). |
| EPA IUR reporting programs | The purpose of the IUR program is to collect quality screening-level, exposure-related information on chemical substances and to make that information available for use by EPA and, to the extent possible, to the public. The IUR data are used to support risk screening, assessment, priority setting and management activities and constitute the most comprehensive source of basic screening-level, exposure-related information on chemicals available to EPA. www.epa.gov/iur/index.html |
| EPIWIN / EPI Suit | Estimations Program's Interface for Windows. www.epa.gov/oppt/exposure/pubs/episuitedi.htm |
| EU TGD spreadsheet | The basis of the EU TGD spreadsheet is multimedia fate model SimpleBox 3.21. SimpleBox determines the distribution and fate of chemicals in the environment in Microsoft Excel. www.cem-nl.eu/eutgd.html |

| Term | Definition |
|--------------------------|--|
| EUSES | EUSES is a decision-support instrument, which enables companies to carry out rapid and efficient assessments of the general risks posed by substances to man and the environment. EUSES is intended mainly for initial and refined risk assessments rather than comprehensive assessments. http://ecb.jrc.ec.europa.eu/euses/ |
| Exposure assessment | Exposure assessment aims to make a quantitative or qualitative estimate of the dose / concentration of the chemical to which humans and the environment are or may be exposed. Exposure assessment is the third step in the process of Risk assessment. |
| Exposure scenario | A set of conditions or assumptions about sources, exposure pathways, amount or concentration of chemicals and exposed organism, or system. This could consider operational conditions and risk management measures, which describe how the chemical is manufactured or used during its life-cycle and how the manufacturer or importer controls, or recommends downstream users to control, exposures of humans and the environment. Important that RMM (risk management measures) are included. |
| GHS | Globally Harmonized System of Classification and Labelling of Chemicals. www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html |
| Good Laboratory Practice | A quality system concerned with the organizational process and the conditions under which analytical, physico-chemical, toxicological and environmental safety studies are planned, performed, monitored, recorded, archived and reported. |
| Hazard characterization | The process of estimation of the incidence and severity of a hazard, if a potential hazard has been identified (see also "hazard identification"). A related term is "dose-response assessment". |
| Hazard identification | The process of determining (i.e. deriving or measuring) the intrinsic hazardous properties of chemicals or mixtures. |
| Impurity | An unintended constituent present in a chemical as manufactured. It may, for example, originate from the starting materials or be the result of secondary or incomplete reactions during the production process. While it is present in the final chemical, it was not intentionally added. In most cases impurities constitute less than 10% of the chemical. |

GLOSSARY

DEFINITION OF TERMS USED IN THIS DOCUMENT

| Term | Definition |
|---|---|
| Intermediate | A chemical that is manufactured for and consumed in or used for chemical processing in order to be transformed into another chemical (referred to as “synthesis”). |
| LC50 (Lethal Concentration x %) | The LC50 corresponds to the concentration of a tested substance causing 50% lethality during a specified time interval. |
| LD50 (Lethal Dose x %) | The LD50 corresponds to the dose of a tested substance causing 50% lethality during a specified time interval. |
| Lowest- observed- adverse-effect level (LOAEL) | The lowest exposure levels at which there are biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group. |
| Mixture, also called preparation | A mixture or solution of two or more chemicals that do not react. |
| MULTICASE | MULTICASE is a commercial QSAR regression model that uses fragments and statistical rules to identify active and inactive fragments, while DEREK is a strictly rule-based commercial program to predict mutagens and non-mutagens. www.multicase.com |
| No Observed Adverse Effect Concentration (NOAEC) | Highest tested concentration at which there are no statistically significant increases in the frequency or severity of adverse effects between the exposed population and an appropriate control group, some effects may be produced at this level, but they are not considered adverse or precursors of adverse effects. |
| No-observed- adverse-effect level (NOAEL) | The highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered adverse effects. |

| Term | Definition |
|-------------------------------------|--|
| OASIS system | <p>OASIS Times for Human Health Endpoints. TIMES (Tissue METabolism Simulator) allows prioritization of chemicals according to toxicity of their metabolites. Presently, TIMES platform is used to predict the following metabolism activated endpoints: Skin sensitization - combining skin metabolism simulator and reactivity model for protein binding, AMES Mutagenicity - combining S9 liver metabolism simulator and reactivity model for DNA binding. Besides the model specifically for TA100, a model of general (across strains) mutagenicity is available. Chromosomal aberration - combining S9 liver metabolism simulator and reactivity model for DNA and protein binding. Receptor mediated endpoints – combining metabolic activation of chemicals in S9 liver and models for binding affinity with ER, AR, and AhR.</p> <p>http://oasis-lmc.org/?section=software&swid=4</p> |
| OECD | <p>Organization for Economic Co-operation and Development.</p> <p>www.oecd.org</p> |
| OECD guidelines | <p>The OECD Guidelines for the Testing of Chemicals are a collection of the most relevant internationally agreed testing methods used by government, industry and independent laboratories to assess the safety of chemical products.</p> <p>www.oecd.org/department/0,3355,en_2649_34377_1_1_1_1_1,00.html</p> |
| OECD SIDS program | <p>The “Screening Information Data Set” (SIDS) program operated under the auspices of the Organization for Economic Cooperation and Development (OECD) is a voluntary cooperative international testing program focused on developing base level test information on international HPV chemicals. The SIDS data are used to “screen” the chemicals and set priorities for further testing or risk assessment/management activities.</p> <p>http://webnet.oecd.org/hpv/ui/Default.aspx</p> |
| OECD Toolbox | <p>The Toolbox is a software application intended to be used by governments, chemical industry and other stakeholders in filling gaps in (eco)toxicity data needed for assessing the hazards of chemicals. The Toolbox incorporates information and tools from various sources into a logical workflow. Crucial to this workflow is grouping chemicals into chemical categories.</p> <p>www.oecd.org/document/54/0,3343,en_2649_34379_42923638_1_1_1_1,00.html</p> |
| Point of Departure (Starting point) | <p>The dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (BMD), or a NOAEL or LOAEL for an observed incidence, or change in level of response.</p> <p>www.epa.gov/NCEA/iris/help_gloss.htm#p</p> |

GLOSSARY

DEFINITION OF TERMS USED IN THIS DOCUMENT

| Term | Definition |
|----------------------------------|---|
| Preparation, also called mixture | See the description of the key term “mixture”. In this document the terms “mixture” and “preparation” are used as equivalent, but the term “mixture” is recommended. |
| Process Category (PROC) | Process category groups together the way a substance is used or converted into a subsequent product (preparation or article). Application techniques or process types have a direct impact on the exposure and hence on the risk management measures needed. |
| REACH | European Community Regulation on chemicals and their safe use. It deals with the Registration, Evaluation, Authorization and Restriction of Chemical substances. |
| REACH Use Descriptor System | The use descriptor system is based on five separate descriptors which in combination with each other form a brief description of use or an exposure scenario title. The sector of use (SU) describes in which sector of the economy the substance is used. This includes manufacture in the chemical industry, mixing of substances at formulator’s level as well as industrial, and professional and consumer end-uses. The chemical product category (PC) describes in which types of preparations (mixtures) the substance is contained on end-use. The process category (PROC) describes the technical process or application in which the substance is used from the occupational perspective. The environmental release category (ERC) describes the broad conditions of use from the environmental perspective. http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm |
| Reference Value | An estimate of an exposure for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime. It is derived from a BMDL, a NOAEL, a LOAEL, or another suitable point of departure, with uncertainty/variability factors applied to reflect limitations of the data used. [Durations include acute, short-term, subchronic, and chronic and are defined individually in this glossary.] [Reference value is a term proposed in the report, “A Review of the Reference Dose and Reference Concentration Processes” (EPA, 2002), and is a generic term not specific to a given route of exposure. EPA develops numerical toxicity values for the RfD and RfC only; no numerical toxicity values are developed for the RfV.] http://www.epa.gov/NCEA/iris/help_gloss.htm#r . In this guidance, the PNEC is defined as a Reference Value for environment because of the consistency. |

| Term | Definition |
|---|---|
| Risk | Risk is the probability that an adverse effect (e.g., skin irritation or cancer) will result from a given exposure to a chemical. The risk posed by a chemical depends both on the intrinsic properties of the chemical (hazard) and on the exposure. |
| Risk assessment | A process intended to calculate or estimate the risk to a given target organism, system or (sub)population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system. The Risk assessment process includes four steps: hazard identification, hazard characterization (related term: dose-response assessment), exposure assessment, and risk characterization. |
| Risk characterization | Risk characterization consists of estimation of the incidence and severity of the adverse effects likely to occur in a human population or environmental compartment due to actual or predicted exposure to a chemical. Risk Characterization is the fourth step in the Risk assessment process. |
| Risk communication | Interactive exchange of information about risks among risk assessors, managers, news media, interested groups, and the general public. |
| Risk evaluation | Establishment of a qualitative or quantitative relationship between risks and benefits, involving the complex process of determining the significance of the identified hazards and estimated risks to those organisms or people concerned with or affected by them. It is the first step in risk management. |
| Risk management | Risk control strategy to reduce hazard and/or exposure by means of substitution, prevention or reduction of emissions and exposure, training, hazard communication etc. thereby reducing the risk to human health or the environment. |
| RISKOFDERM Dermal model (higher tool) | Risk Assessment of Occupational Dermal Exposure to Chemicals. |
| Sister Chromatid Exchange Assay (SCE) | The sister chromatid exchange (SCE) assay is a widely used method for assessing chromosome breakage and repair, though it is much more commonly conducted as an in vitro test. Methodology for the in vitro assay is described in OECD Test Guideline 479, but there is no recommended methodology for the in vivo assay. www.oecd.org/dataoecd/39/12/34446120.pdf |

GLOSSARY

DEFINITION OF TERMS USED IN THIS DOCUMENT

| Term | Definition |
|--|---|
| T25 | The chronic dose rate that will give 25% of the animals' tumours at a specific tissue after correction for spontaneous incidence, within the life time of that species. |
| Threshold of effect | The exposure level or dose of an chemical above which toxicity or adverse health effects can occur, and below which toxicity or adverse health effects are unlikely). |
| TOPKAT | QSAR based program. TOPKAT can be used for tests including physical/chemical, environmental fate, ecotoxicity, toxicity, mutagenicity, and subchronic reproductive/developmental. www.accelrys.com/products/topkat/index.html |
| Toxicology | Toxicology (from the Greek words Τοξικός - toxicos "poisonous" and logos is the study of the adverse effects of chemicals on living organisms. It is the study of symptoms, mechanisms, treatments and detection of poisoning, especially the poisoning of people. |
| US EPA Sustainable Futures Initiative (SF) | Offers a variety of computer-based models for human /environmental exposure estimation. www.epa.gov/oppt/sf/ |
| Use and exposure category | An exposure scenario covering processes or uses that present similar exposure characteristics. |

NOTE: the section on "the definition of terms used in this document" do not represent an official definition used by ICCA member companies but merely serves the objective to provide more information on the complex terminology (including references).

ANNEX 1

ALTERNATIVE RISK ASSESSMENT METHODS

Table 16: Alternative guidance for chemical risk assessment

| Organization / Region | Source |
|-----------------------|---|
| ECB | http://ecb.jrc.it/documents/TECHNICAL_GUIDANCE_DOCUMENT/EDITION_2/tgdpart2_2ed.pdf |
| IPCS | www.inchem.org/pages/about.html |
| Japan | www.env.go.jp/chemi/communication/senmon.html www.mhlw.go.jp/bunya/roudoukijun/anzeneisei14/index.html www.safe.nite.go.jp/english/index.html www.safe.nite.go.jp/english/ghs/pdf/guidance_e.pdf http://unit.aist.go.jp/riss/crm/index_e.html |
| OECD | www.oecd.org/department/0,3355,en_2649_34373_1_1_1_1_1,00.html |
| REACH | http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm |
| US EPA | www.epa.gov/risk |
| WHO | www.who.int/ipcs/methods/en |

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ANNEX 3

REFERENCES

- ¹ For more information on the Global Charter, see www.icca-chem.org
- ² For more information on ICCA guidance documents, see www.icca-chem.org
- ³ OECD Decision on Mutual Acceptance of Data, 1981
- ⁴ Klimisch, H.-J., Andreae, M., and Tillmann, U. 1997 A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regul. Toxicol. Pharmacol.* 25, 1–5
- ⁵ www.epa.gov/HPV/pubs/general/datadfin.htm
- ⁶ www.inchem.org/documents/ehc/ehc/ehc214.htm
- ⁷ *Regul Toxicol Pharmacol* 25(1):1-5 (1997)
- ⁸ OECD Decision on Mutual Acceptance of Data, 1981
- ⁹ UN Manual for Tests and Criteria for physical hazards– United Nations, New York and Geneva 2003. ISBN 92-1-13
www.unece.org/trans/danger/publi/ghs/ghs_rev02/English/02e_part2.pdf
- ¹⁰ www.oecd.org/department/0,3355,en_2649_34365_1_1_1_1_1,00.html
- ¹¹ www.iso.org/iso/home.htm
- ¹² www.ich.org/cache/compo/276-254-1.html
- ¹³ www.astm.org
- ¹⁴ <http://ecb.jrc.ec.europa.eu>
- ¹⁵ www.epa.gov/oppt
- ¹⁶ www.meti.go.jp/english/information/data/TESTindex.html
- ¹⁷ For additional guidance on grouping of chemicals see www.oecd.org/dataoecd/53/62/39850072.pdf
- ¹⁸ www.oecd.org/dataoecd/39/12/34446120.pdf
- ¹⁹ http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r6_en.pdf?vers=20_08_08
- ²⁰ www.oecd.org/dataoecd/33/41/37850114.pdf
- ²¹ UN Manual for Tests and Criteria for physical hazards– United Nations, New York and Geneva 2003. ISBN 92-1-139087-7
- ²² Derivation of Assessment Factors for Human Health Risk Assessment, 2003
- ²³ Guidance on information requirements and chemical safety assessment (May 2008) Table R.8-6.

- ²⁴ For details, refer to chapter R.10 in the Guidance on Information Requirements and Chemical Safety Assessment of REACH.
- ²⁵ Available QSAR or read-across/category data may be used. For more guidance see:
http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r6_en.pdf?vers=20_08_08
- ²⁶ www.epa.gov/nrmrl/std/cppb/qsar/index.html#TEST
- ²⁷ www.multicase.com/
- ²⁸ www.lhasalimited.org/
- ²⁹ www.accelrys.com/products/topkat/index.html
- ³⁰ www.compudrug.com
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- ³² http://iccvam.niehs.nih.gov/methods/acutetox/inv_nru_brd.htm
- ³³ www.oecd.org/dataoecd/39/12/34446120.pdf
- ³⁴ www.ncbi.nlm.nih.gov/pubmed/16522150
- ³⁵ www.springerprotocols.com/Abstract/doi/10.1385/1-59745-037-5:371
- ³⁶ www.ncbi.nlm.nih.gov/pubmed/15588167
- ³⁷ www.ncbi.nlm.nih.gov/pubmed/15588168
- ³⁸ www.oecd.org/document/54/0,3343,en_2649_34379_42923638_1_1_1_1,00.html
- ³⁹ <http://chm.pops.int/>
- ⁴⁰ www.pbtprofiler.net/
- ⁴¹ US NRC, 1991a.
- ⁴² http://ec.europa.eu/competition/mergers/cases/index/nace_all.htm
- ⁴³ www.oecd.org/document/46/0,3343,en_2649_34373_2412462_1_1_1_1,00.html
- ⁴⁴ www.ecetoc.org/tra
- ⁴⁵ http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_part_d_en.pdf
- ⁴⁶ www.cefic.org/files/downloads/RMM%20Library%20.xls
- ⁴⁷ <http://reach.bdi.info/378.htm>
- ⁴⁸ <http://reporting.responsiblecare-us.com/Search/PSSummarySearch.aspx>
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