INTERNATIONAL
COUNCIL OF
CHEMICAL
ASSOCIATIONS

Global Product Strategy

ICCA Guidance on Chemical Risk Assessment

Product Stewardship in action:
Sound chemicals management is a global responsibility

2nd Edition - 2011

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.

Risk assessments conducted under GPS do not constitute a new safety standard. ICCA and its member associations accept no liability and assume no responsibility with regard to the contents of this document or the accuracy, completeness or usefulness of any information or process in this document, or its application by any person, including liability or responsibility to any third party. Users are reminded that although the guide tries to provide an easier roadmap to risk assessment it will still require significant toxicological and ecotoxicological expertise to conduct a risk assessment. The use of a professional toxicologist to interpret the results is highly recommended.

Antitrust and Competition Compliance

Companies who use this guidance must be aware that antitrust and competition laws may apply for some activities conducted by companies together.

Therefore, the need of compliance is essential as for any activity conducted by ICCA. ICCA has published an Antitrust and Competition Law Guide which all users are encouraged to read before starting activities and refer to while conducting activities.

DO NOT presume that by reading this Guide you know everything about antitrust/competition law.
It is neither exhaustive, nor a substitute for legal advise. In case of questions or doubts consult your company lawyer, well in time. Always remember ignorance is not an excuse with antitrust/competition authorities.

DO NOT engage in prohibited activities at the occasion of activities made in application of this document, or at the occasion of social gatherings incidental to your lawful activities

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 Charter[1]. 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 met[2].

Resources are a key factor especially for small and mid-sized companies (SMEs) in emerging economies as well as in developed regions when implementing GPS and performing chemical risk assessments. Many companies have no or very limited experience in risk assessment and related methodologies. An important objective is therefore to find ways for associations and larger companies to support SMEs. As a response ICCA has developed a set of guidance materials for risk assessment and risk management as part of its GPS implementation efforts.

The GPS risk assessment guidance particularly addresses small and medium sized enterprises in emerging economies which may need assistance in the assessment of chemicals regarding their hazardous and exposure potential and to develop risk management measures for safe handling of substances throughout their life cycle (incl. value chain activities).

The goal was to come up with an easy to use stepwise process as a first step to bridge gaps in current performance. The GPS guidance is intended to be simple and pragmatic: a first step for beginners in risk assessment to bring them from "school level" to advanced "bachelor" knowledge. More detailed technical guidance to advance to an expert "PhD" level can subsequently be obtained (and understood) from other sources such as guidance documents developed at OECD or in OECD member countries. It simply provides a basis on general methodology of risk assessment but is not intended to replace the requirements of various national and regional regulations in force.

The document is divided into two main sections – each comprising 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 and how to communicate the outcome. The completion of each step prepares the reader for the next step. 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 and sources for alternative information are provided at the end of the document.

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 9 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 by considering both the hazard and the exposure together. 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 185 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 55)

Exposure assessment: identifying the extent to which exposure actually occurs (see page 106)

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 132). 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

STEP 1: Select Substances for Risk Assessment

↓

STEP 2: Gather all available information from internal and external sources on hazard and exposure

↓

STEP 3: Allocate Substances to Priorities

↓

Priority 1 **High Exposure** **or** **High Hazard** **potential**	**Priority 2** **Medium Exposure** **or** **Medium Hazard** **potential**	**Priority 3** **Low Exposure** **or** **Low Hazard** **potential**	**Priority 4** **Very Low Exposure** **or** **Very Low Hazard**
Top priority for RA	2nd priority for RA	3rd priority for RA	No further action needed

↓

STEP 4: Complete Priority Relevant Information

↓

STEP 5: Hazard Characterization   **STEP 6: Exposure Assessment**

↕ iterative process

STEP 7: Risk Characterization

↓

STEP 8: Document outcome company internally (risk assessment report) and share relevant information with the public (GPS safety Summary)

SECTION ONE PREPARATION

In Section One you will gather the data necessary to conduct the actual assessment as described in Section Two.

If you compare the steps in this guidance to cooking a meal, Section One explains to the user where and which ingredients need to be gathered whereas Section Two explains how to cook the dish. However, similar to preparing a meal a chemical risk assessment is not a one-way street it is an iterative process, which involves researchers continuously identifying and filling data gaps in order to develop a more refined assessment of the risk. The same goes for your meal, you might need to go back to the beginning and add more ingredients or refine the flavor by adding additional spices to the procedure. There might be several circles of assessment necessary before you can conclude that the substance can be handled safely.

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 different priorities 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 Priorities in order to prioritize them for risk assessment
>
> **STEP 4:** Complete Priority-relevant information in order to ensure the appropriate level of information (Base Set of information) 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 "Priorities" according to an initial consideration of their hazard and / or exposure potential. Each Priority is associated with a set of information needed for risk assessment. Chemicals with higher hazard and / or exposure potential (e.g. those allocated to Priority 1) would be risk assessed first. These chemicals also need more information as a staring point for their risk assessment than chemicals with lower hazard or exposure potential (e.g. Priority 4).

PLEASE NOTE:

(1) Just because a chemical is allocated to Priority 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 185).

(3) The same scientific principles apply when assessing the toxicity of a mixture as for single chemical characterisation (for more information please refer to Addendum 1, page 154). Mixture in the context of the GPS risk assessment refers to a preparation (sold into commerce) composed of two or more substances.

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 no GPS-specific Risk Assessments has to be conducted as already covered by other regulatory programs

- 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

* While certain information such as results from toxicity testing can be exchanged between copanies your companies product portfolio should not be disclosed or discussed due to antitrust / competition law compliance. DO NOT discuss chemicals on this list with other companies. For more information on antirust / 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 18 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 adequacy 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 countries[3]. For more information on how to assess whether the information is reliable, see page 22 and refer to the Klimisch code[4] or US EPA criteria[5]:

(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 18-21.

Table 1: Standard Parameters of Chemical Substances

NOTE: In case one of the parameters is not appropriate (e.g. acute toxicity to fish or daphnia for a gas) proper justification for the exemption should be provided.

Standard Parameter	Description
Chemical Identity and use	• CAS Number(s) • Name • Structural Formula • Composition of the chemicals (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. • Molecular weight
Classification and labeling information	• Physical hazard; Health hazard; Environmental hazard
Physical-Chemical Properties	• 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 (algea or 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 18. 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 9).

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 acceptable and to be encouraged (see page 44). Where appropriate use non-animal methods first. 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: Example Hazard Endpoints

Human Health
- Acute toxicity (skin / oral / inhalation)
- Eye / Skin irritation and corrosivity (when gathering new information non-animals methods are recommended)
- Sensitization (when gathering new information non-animals methods are recommended)
- 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
- pH

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 agents[6].

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 104 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 20. Based on this information, you will be able to assign potential for exposure of the chemical and prioritize it for assessment (see page 28).

Gather information on the following areas (see page 106 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	
GHS	http://live.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html http://www.safe.nite.go.jp/english/ghs_index.html

Sources for Phys.-Chem Information	
Beilstein Database	www.stn-international.com/beilstein_substance.html?&L=0&cHash=
CRC Handbook of Chemistry and Physics	www.hbcpnetbase.com/
Illustrated Handbooks of Physico-Chemical Properties and Environmental Fate for Organic Chemicals.	http://www.cabi.org/default.aspx?site=170&page=1029
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	
ACToR	http://www.epa.gov/actor/
Concise International Chemicals Assessment Document (CICAD)	www.inchem.org/pages/cicads.html
DSSTox	http://www.epa.gov/ncct/dsstox/index.html
ECOTOX Database	http://cfpub.epa.gov/ecotox/
E-SovTox database	http://kbfi-databases.eu/database/
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
International Agency for Research on Cancer (IARC) Publications	www.iarc.fr/en/publications/index.php

Sources for Hazard Information (cont)	
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/riskhykdl01.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://www.oecd.org/ehs/eChemPortal
ORATS (Online European Risk Assessment Tracking System) ESIS (European Chemical Substance Information System)	http://esis.jrc.ec.europa.eu/
REACH information on registered substances	http://apps.echa.europa.eu/registered/registered-sub.aspx
Recommendation of Occupational Exposure Limits issued by Japan Society for Occupational Health	http://joh.med.uoeh-u.ac.jp/oel/index.html
Risk assessment portal	www.epa.gov/risk/guidance.htm
Threshold Limit Values of ACGIH (fee required)	www.acgih.org/store/
Toxic Substance Control Act Test Submission Database	www.syrres.com/esc/tscats.htm
Toxics Release Inventory (TRI)	http://www.epa.gov/enviro/html/tris/tris_query.html
ToxRefDB	http://www.epa.gov/ncct/toxrefdb/
US EPA High Production Volume Information System (HPVIS)	http://www.epa.gov/hpv/hpvis/index.html
US EPA HPV database	http://www.epa.gov/hpvis/
US EPA Integrated Risk Information System (IRIS)	http://www.epa.gov/iris/
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
American Cleaning Institute	http://www.aciscience.org/Portals/0/docs/Consumer_Product_Ingredient_Safety_v2.0.pdf
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)	The European Chemicals Agency has developed a 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
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	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 Priority 1 assessment is only valid for inhalation exposure. www.reach-clp-helpdesk.de/reach/en/Exposure/Exposure.html

Sources for Exposure Information (cont)	
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
Household Products Database	The database (content not routinely updated) is designed to help answer the following typical questions: • 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? http://hpd.nlm.nih.gov/index.htm
Sector groups have developed use descriptors typical for their sector	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
Occupational Exposure to Hazardous Agents (Haz-Map)	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. http://hazmap.nlm.nih.gov/

How to assess information for reliability, relevance and adequacy

Reliable evidence linking a chemical to a resulting effect can be obtained from statistically controlled studies and workplace evaluations on humans and additional human experience.

When data from human studies are not available, then data from animal studies or other sources are relied upon to draw inference about potential hazard to humans. These include non-test information (such as QSARs), in chemico and in vitro studies and in vivo animal tests.

No information should be removed from consideration, but assessment of reliability, relevance, and adequacy should be used to judge the applicability of any information in a weight of evidence evaluation.

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 system[7] 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 countries[8]. High quality test data for substances and mixtures of physical hazards can be produced in accordance with internationally recognized test guidelines[9]. 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 Guidelines[10]
  http://www.oecd.org/env/testguidelines

- International Standard Organization (ISO) Guidelines[11]
  www.iso.org/iso/home.htm

- International Conference of Harmonization (ICH) Guidelines[12]
  www.ich.org/

- ASTM International[13]
  www.astm.org

- European Union Test Methods Regulation No. 440/2008[14]
  http://echa.europa.eu/legislation/reach_legislation_en.asp

- US Environmental Protection Agency[15]
  www.epa.gov/oppt/

- METI (Japan)[16]
  www.meti.go.jp/english/information/data/TESTindex.html

STEP 3: ALLOCATE SUBSTANCES INTO PRIORITIES

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 Priorities (see figure 2, page 28).

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

  In the workplace, along the supply chain, or to consumers.
  See Table 4, page 42 to help answer this question.

- **Allocate chemicals into Priorities**

  The prioritisation as proposed by GPS is intended to provide guidance to countries where no regulatory prioritisation or framework for determining the safety of chemicals is place. It is not intended to replace legaly required prioritisation procedures. GPS prioritises the chemicals for risk assessment based on their hazard or exposure potential. The Priority-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 Priority System.

The Priority System

The GPS Priority system is based on a hazard / exposure rating (see figure 2 page 28). 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 Priorities 1 and 2 for priority assessment. Substances with low to very low hazard and / or exposure potential are allocated to Priorities 3 and 4 for low priority risk assessment.

> REMINDER: The aim of the prioritisation is to decide which chemical in your portfolio to assess first (in case no regulatory requirements apply). Chemicals with a high hazard or high exposure potential should be assessed first. Being high priority does however not imply that the current production, handling and use of the chemical is not safe. In most cases the conclusion of the subsequent risk assessment will 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. 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. The calculation of risk will be explained later in Section Two, Step 7 (see page 140).

Priority 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.

Priority 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.

Priority 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.

Priority 4: These substances are of minimum priority as they have minimum 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, Priority 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.

STEP 3: ALLOCATE SUBSTANCES INTO PRIORITIES

Allocating Substances into Risk Assessment Priorities: Process

Figure 2: Decision Tree for allocating Substances into Priorities

Figure 2: Decision Tree for allocating Substances into Priorities
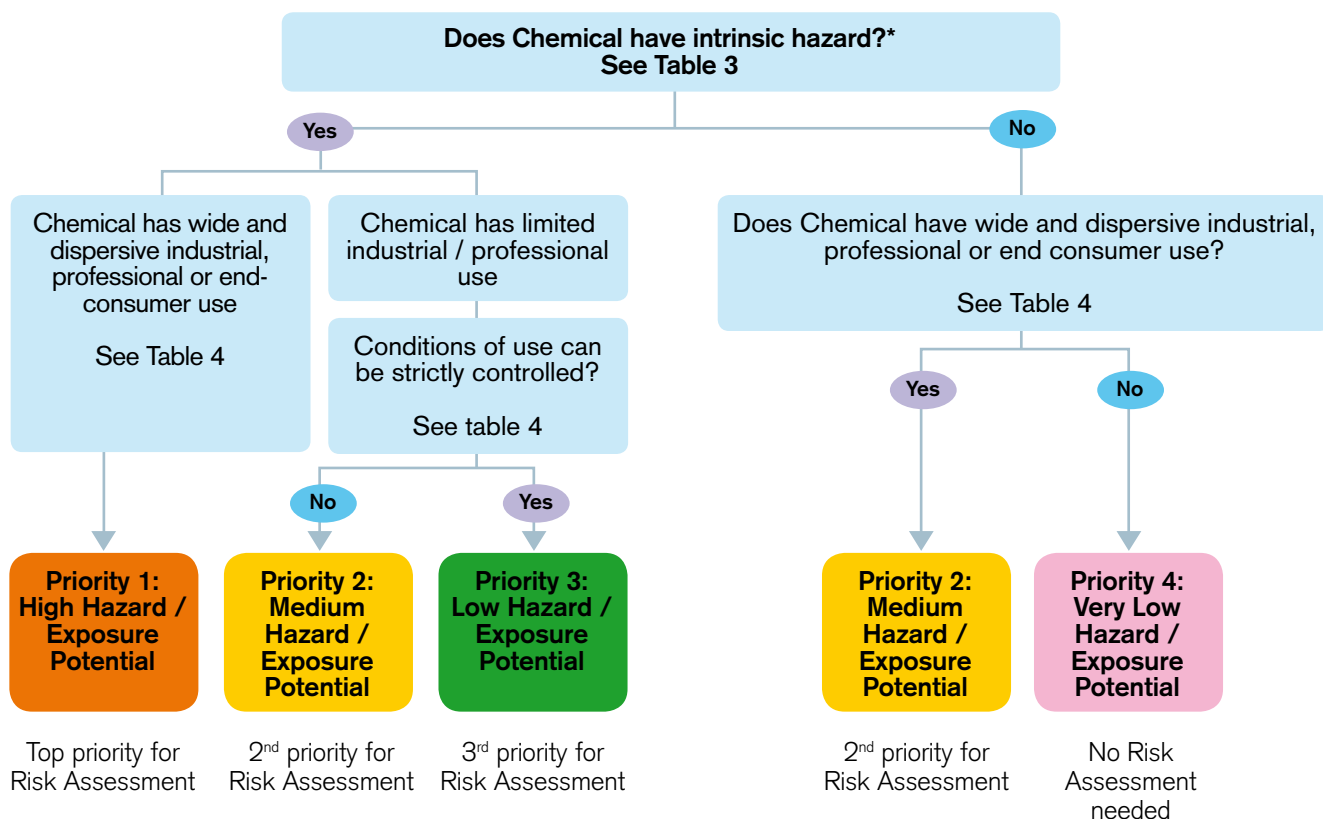
* Check whether chemical is on Regulatory Candidate Lists (e.g. Annex XIV of the REACH Regulation). If yes, then follow legal requirements

Figure 2 summarizes the decision making process to follow in order to allocate substances into Priorities. 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 30. 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. GHS and GPS both depend on toxicological data (animal or alternative data) for hazard assessments, i.e. have common roots. However, the final outcomes are slightly different: While GHS leads to the classification and labelling of substances based on their hazards, GPS arrives at a chemical risk assessments: which means goes one step further and also takes exposure levels into account. This means the initial step of GHS and GPS is the same, gather and evaluate the hazard data but GPS then requires manufacturers to in addition gather information on use and application to judge the potential risk of a chemical based on hazard and exposure.

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 110). 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 at the same time. Each endpoint will be weighed seperately. Therefore in the decision tree you should follow the purple column (yes route).

Allocate substances into Priorities

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

Priority 1 =	Priority 2 =	Priority 3 =	Priority 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 76)
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
Priority allocation system (based on information that may already exist on your
substance to help with prioritization)

a) Human health (based on GHS classification criteria)

Hazard Endpoint: Acute Tox (skin / oral / inhalation)

Hazardous Level 1	Hazardous Level 2
Decision Yes	**Decision** Yes
UN GHS Cat 1 LD50 ≤ 5 mg/kg bw/d (oral) LD50 ≤ 50 mg/kg bw/d (skin/dermal) LC50 ≤ 100 ppm (gas) LC50 ≤ 0.5 (mg/L) (vapour) LC50 ≤ 0.05 (mg/L) (dust, mist)	UN GHS Cat 2/3 LD50 > 5 ≤ 300 mg/kg bw/d (oral) LD50 > 50 ≤ 1000 mg/kg bw/d (skin/dermal) LC50 > 100 ≤ 2500 ppm (gas) LC50 > 0.5 ≤ 10.0 (mg/L) (vapour) LC50 > 0.05 ≤ 1 (mg/L) (dust, mist)

Hazardous Level 3	Hazardous Level 4
Decision No	**Decision** No
UN GHS Cat 4 LD50 > 300 ≤ 2000 mg/kg bw/d (oral) LD50 > 1000 ≤ 2000 mg/kg bw/d (skin/dermal) LC50 > 2500 ≤ 5000 ppm (gas) LC50 > 10.0 ≤ 20.0 (mg/L) (vapour) LC50 > 1.0 ≤ 5.0 (mg/L) (dust, mist)	UN GHS Cat 5 LD50 > 2000 ≤ 5000 mg/kg bw/d (oral or skin/dermal) For gases, vapours, dusts, mists, LC50 in the equivalent range of the oral and dermal LD50 (i.e., 2000 and 5000 mg/kg bw/d)

a) Human health (based on GHS classification criteria)

Hazard Endpoint: Skin Corrosion / Irritation

Hazardous Level 1	Hazardous Level 2
Decision Yes	**Decision** Yes
Corrosive UN GHS Cat 1 A/B/C For substances and tested mixtures: • Human experience showing irreversible damage to the skin; • Structure/activity or structure property relationship to a substance or mixture already classified as corrosive; • pH extremes of 2 and 11.5 including acid/alkali reserve capacity; • Positive results in a valid and accepted in vitro skin corrosion test; or • Animal experience or test data that indicate that the substance/mixture causes irreversible damage to the skin following exposure of up to 4 hours. For mixtures where substances can be added: • Classify as corrosive if the sum of the concentrations of corrosive substances in the mixture is ≥ 5% (for substances with additivity); or For mixtures where substances cannot be added: ≥ 1%.	**Irritant** UN GHS Cat 2 For substances and tested mixtures: • Human experience or data showing reversible damage to the skin following exposure of up to 4 hours; • Structure/activity or structure property relationship to a substance or mixture already classified as an irritant; • Positive results in a valid and accepted in vitro skin irritation test; or • Animal experience or test data that indicate that the substance/mixture causes reversible damage to the skin following exposure of up to 4 hours, mean value of ≥ 2.3 < 4.0 for erythema/eschar or for oedema, or inflammation that persists to the end of the observation period, in 2 of 3 tested animals. For mixtures where substances can be added: • The sum of concentrations of corrosive substances in the mixture is ≥ 1% but ≤ 5%; • The sum of the concentrations of irritant substances is > 10%; or • The sum of (10 × the concentrations of corrosive ingredients) + (the concentrations of irritant ingredients) is ≥ 10%; or For mixtures where substances cannot be added: ≥ 3%.

Hazardous Level 3	Hazardous Level 4
Decision No	**Decision** No
Mild Irritant UN GHS Cat 3 For substances and tested mixtures: • Animal experience or test data that indicates that the substance/mixture causes reversible damage to the skin following exposure of up to 4 hours, mean value of $\geq 1.5 < 2.3$ for erythema/eschar in 2 of 3 tested animals For mixtures where substances can be added: • The sum of the concentrations of irritant substances in the mixture is $\geq 1\%$ but $\leq 10\%$; For mixtures where substances cannot be added: • The sum of the concentrations of mild irritant substances is $\geq 10\%$; • The sum of ($10 \times$ the concentrations of corrosive substances) + (the concentrations of irritant substances) is $\geq 1\%$ but $\leq 10\%$; or • The sum of ($10 \times$ the concentrations of corrosive substances) + (the concentrations of irritant substances) + (the concentrations of mild irritant substances) is $\geq 10\%$.	**Non irritating**

a) Human health (based on GHS classification criteria)

Hazard Endpoint: Eye Irritation

Hazardous Level 1	Hazardous Level 2
Decision Yes	**Decision** Yes
Irreversible Effects UN GHS Cat 1 For substances and tested mixtures • Classification as corrosive to skin; • Human experience or data showing damage to the eye which is not fully reversible within 21 days; • Structure/activity or structure property relationship to a substance or mixture already classified as corrosive; • pH extremes of < 2 and > 11.5 including buffering capacity; • Positive results in a valid and accepted in vitro test to assess serious damage to eyes; or • Animal experience or test data that the substance or mixture produces either (1) in at least one animal, effects on the cornea, iris or conjunctiva that are not expected to reverse or have not reversed; or (2) in at least 2 of 3 tested animals a positive response of corneal opacity ≥ 3 and/or iritis > 1.5. For mixtures where substances can be added: • Classify as Category 1 if the sum of the concentrations of substances classified as corrosive to the skin and/or eye Category 1 substances in the mixture is ≥ 3%; or For mixtures where substances cannot be added: ≥ 1.	**Irritant** UN GHS Cat 2A For substances and tested mixtures • Classification as severe skin irritant; • Human experience or data showing production of changes in the eye which are fully reversible within 21 days; • Structure/activity or structure property relationship to a substance or mixture already classified as an eye irritant; • Positive results in a valid and accepted in vitro eye irritation test; or • Animal experience or test data that indicate that the substance/mixture produces a positive response in at least 2 of 3 tested animals of: corneal opacity ≥ 1, iritis ≥ 1, or conjunctival edema (chemosis) ≥ 2. For mixtures where substances can be added: • The sum of the concentrations of skin and/or eye Category 1 substances in the mixture is ≥ 1% but ≤ 3%; the sum of the concentrations of eye irritant substances is ≥ 10%; or • The sum of (10 × the concentrations of skin and/or eye category 1 substances) + (the concentrations of eye irritants) is ≥ 10%; or For mixtures where substances cannot be added: • The sum of the concentrations of eye irritant ingredients is 3%.

Hazardous Level 3	Hazardous Level 4
Decision No	**Decision** No
Mild Irritant UN GHS Cat 2B For substances and tested mixtures; • Human experience or data showing production of mild eye irritation; • Animal experience or test data that indicate that the lesions are fully reversible within 7 days. For mixtures where substances can be added: t • The sum of the concentrations of skin and/or eye Category 1 substances in the mixture is ≥ 1% but ≤ 3%; • The sum of concentrations of eye irritant substances is ≥ 10%; or • The sum of (10 × the concentrations of skin and/or eye category 1 substances) + (the concentrations of eye irritants) is ≥ 10%; or For mixtures where substances cannot be added: • The sum of the concentrations of eye irritant ingredients is ≥ 3%.	**Non irritating**

a) Human health (based on GHS classification criteria)

Hazard Endpoint: Sensitization

Hazardous Level 1	Hazardous Level 2
Decision Yes	**Decision** Yes
UN GHS Cat 1 Respiratory For substances and tested mixtures: • If there is human evidence that the individual substance induces specific respiratory hypersensitivity, and/or Where there are positive results from an appropriate animal test. • If any individual respiratory sensitizer in the mixture has a concentration of: ≥ 1.0% Solid/Liquid ≥ 0.2% Gas	UN GHS Cat 1 Skin For substances and tested mixtures: • If there is evidence in humans that the individual substance can induce sensitization by skin contact in a substantial number of persons, or Where there are positive results from an appropriate animal test. • If any individual skin sensitizer in the mixture has a concentration of: ≥ 1.0% Solid/Liquid/Gas

Hazard Endpoint: Mutagenicity / Carcinogenicity

Hazardous Level 1	Hazardous Level 2
Decision Yes	**Decision** Yes
UN GHS Cat 1 A/B • Known to induce heritable mutations or regarded as if it induces heritable mutations in the germ cells of humans or mixtures containing ≥ 0.1% of such a substance. • Known or presumed human carcinogen including mixtures containing ≥ 0.1% of such a substance.	UN GHS Cat 2 • Causes concern for man owing to the possibility that it may induce heritable mutations in the germ cells of humans or mixtures containing ≥1.0% of such a substance. • Suspected human carcinogen including mixtures containing more than ≥ 0.1 or ≥1.0% of such a substance.

Hazardous Level 3	Hazardous Level 4
Decision No	**Decision** No
Not sensitizing	Not sensitizing

Hazardous Level 3	Hazardous Level 4
Decision No	**Decision** No
Not suspected to be mutagenic / carcinogenic	Not suspected to be mutagenic / carcinogenic

a) Human health (based on GHS classification criteria)

Hazard Endpoint: Repeated dose (skin / oral / inhalation)

Hazardous Level 1	Hazardous Level 2
Decision Yes	**Decision** Yes
UN GHS Cat 1 • Reliable evidence on the substance or mixture (including bridging) of an adverse effect on specific organ/systems or systemic toxicity in humans or animals. May be named for specific organ/system. • Mixture that lacks sufficient data, but contains Category 1 ingredient: ≥ 1 to ≤ 10% for some authorities; and ≥ 10% for all authorities. NOEL ≤ 30 mg/kg bw/d	UN GHS Cat 2 • Evidence on the substance or mixture (including bridging) of an adverse effect on specific organ/systems or systemic toxicity from animal studies or humans. May be named for specific organ/system. • Mixture that lacks sufficient data, but contains Category 1 ingredient: ≥ 1.0 but ≤ 10% for some authorities and/or contains Category 2 ingredient: ≥ 1.0 or ≥ 10%. NOEL > 30 ≤ 300 mg/kg bw/d

Hazard Endpoint: Repro / Develop (skin / oral / inhalation)

Hazardous Level 1	Hazardous Level 2
Decision Yes	**Decision** Yes
UN GHS Cat 1 A/B • Known or presumed human reproductive toxicants or mixtures containing ≥ 0.1% or ≥ 0.3 % of such a substance. NOEL ≤1 mg/kg bw/d	UN GHS Cat 2 • Suspected human reproductive toxicants or mixtures containing ≥ 0.1% or ≥ 3.0 % of such a substance. NOEL > 1 ≤ 100 mg/kg bw/d

Hazardous Level 3	Hazardous Level 4
Decision No	**Decision** No
NOEL > 300 ≤ 1000 mg/kg bw/d	No effect found at the highest tested dose (1000 mg/kg bw/d)

Hazardous Level 3	Hazardous Level 4
Decision No	**Decision** No
NOEL > 100 ≤ 1000 mg/kg bw/d	No effect found at the highest tested dose (1000 mg/kg bw/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	UN GHS Cat 1 For substances and tested mixtures: $L(E)C50 \leq 1mg/L$ where L(E)C50 is either fish 96hr LC50, crustacea 48hr EC LC50 or aquatic plant 72 or 96hr ErC50	UN GHS Cat 2 For substances and tested mixtures: $1mg/L < L(E)C50 \leq 10mg/L$ where L(E)C50 is either fish 96hr LC50, crustacea 48hr EC LC50 or aquatic plant 72 or 96hr ErC50	UN GHS Cat 3 For Substances and tested mixtures: $10mg/L < L(E)C50 \leq 100mg/L$ where L(E)C50 is either fish 96hr LC50, crustacea 48hr EC LC50 or aquatic plant 72 or 96hr ErC50	No classification No acute toxicity
Chronic toxicity	UN GHS Cat 1 For substances: • $L(E)C50 \leq 1mg/L$; and • Lack the potential to rapidly biodegrade and/or have the potential to bioaccumulate ($BCF \geq 500$ or if absent log Kow ≥ 4) where L(E)C50 is either fish 96hr LC50, crustacea 48hr EC LC50 or aquatic plant 72 or 96hr ErC50	UN GHS Cat 2 For substances: • $1 mg/L < L(E)C50 \leq 10 mg/L$; and • Lack the potential to rapidly biodegrade and/or have the potential to bioaccumulate ($BCF \geq 500$ or if absent log Kow ≥ 4); unless • Chronic NOECs $> 1mg/L$	UN GHS Cat 3 For substances: • $10 mg/L < L(E)C50 \leq 100 mg/l$; and • Lack the potential to rapidly biodegrade and/or have the potential to bioaccumulate ($BCF \geq 500$ or if absent log Kow ≥ 4); unless • Chronic NOECs $> 1mg/L$	UN GHS Cat 4 For substances: • Poorly soluble and no acute toxicity is observed up the water solubility • Lack the potential to rapidly biodegrade and have the potential to bioaccumulate ($BCF \geq 500$ or if absent log Kow ≥ 4); unless • Chronic NOECs $> 1mg/L$
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	Not applicable	Not PBT
Bioaccumulation	BCF > 5000 L/kg	BCF > 2000 L/kg	Not applicable	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 explode 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 Yes	Decision Yes	Decision No	Decision No
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 crafts-man); 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 ad-hesive and other coating) PROC11 (Spray-ing 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 for-mulation of prepara-tions and articles (multistage and/or significant contact)) PROC6 (Calendering operations) PROC7 (Spraying in industrial settings and applications) PROC8b (Transfer of substance or prepa-ration (charging/ discharging) from/ to vessels/large containers at non dedicated facilities) 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 Yes	Decision Yes	Decision No	Decision No
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)*	ERC8a (Wide dispersive indoor use of processing aids in open-systems) ERC8b (Wide dispersive indoor use of reactive substances in open-systems) ERC8d (Wide dispersive outdoor use of processing aids in open-systems) ERC8e (Wide dispersive outdoor use of reactive substances in open-systems) 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) 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)	ERC8c (Wide dispersive indoor use of substances which will be bound into or onto a matrix or material) ERC8f (Wide dispersive outdoor use of substances which will be bound into or onto a matrix or material) ERC9a (Wide dispersive indoor use of reactive substances in open-systems) ERC9b (Wide dispersive outdoor use of reactive substances in open-systems) ERC10a (Wide dispersive outdoor use of substances included into or onto articles and materials that have a long service life with low-release) ERC11a (Wide dispersive indoor use of substances included into or onto articles and materials that have a long service life with low-release)	ERC2 (Formulation of preparations) ERC3 (Formulation in materials) ERC4 (Used as processing aids in production or processes and not made into finished products) ERC5 (Use of substances that are bound into or onto a matrix or material)	ERC1 (Production of chemicals) ERC6a (Use of intermediates) ERC6b (Use of reactive processing aids) ERC6c (Use of monomers in the production of polymers) ERC6d (Use of processing aids in the production of polymers and rubbers) ERC7 (Use of substances in closed-systems)

STEP 4: DEVELOP PRIORITY-RELEVANT INFORMATION ("BASE SET OF INFORMATION")

In Step 4 you will be shown how to:

- **Identify exemptions:** some chemicals possess certain intrinsic properties (e.g. phys-chem.) that prevents them to be tested for some of the endpoints required in the base set. In Box 5 (page 45) alternative approaches to testing or alternatives to standard testing procedures are presented that could still meet the information requirements of the base set.

- **Gather Priority-relevant information:** in order to conduct a risk assessment on each chemical according to its Priority 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 GPS system is that it defines the degree of information (the "Base Set") that serves as a starting point for the risk assessment 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 Priority-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, Priority 1 substances have the highest Base Set of information requirement whilst Priority 4 substances have the lowest. In general, Priority 4 substances only require the level of information already gathered in Step 2 plus additional minimal information in case of accidental exposure, see page 49. On the other hand, more information – over and above that explained in this guidance document may be required for Priority 1 substances.

(3) The GPS Base Set of information is specific for each Priority 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 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 Priority.

GPS Base Set

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 Priority allocation of the chemical. Once complete, we call the information gathered the "***GPS Base Set***".

> GPS Base Set = Standard Parameters (Step 2) + Priority-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. For more information on weight of evidence see page 55.

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

- For chemicals which have an 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. Additional guidance can be found in the US EPA Product Properties Test Guidelines OPPTS (http://fedbbs.access.gpo.gov/library/epa_830/830-7950.pdf)

- 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

STEP 4: DEVELOP PRIORITY-RELEVANT INFORMATION ("BASE SET OF INFORMATION")

- Testing not necessary: Sometimes there is little additional benefit to be gained from conducting a test if information from other tests indicates a particular property. For example, within REACH it is accepted that if a substance is a genotoxic carcinogen then there is no need to test for reproductive toxicity (because appropriate risk measures need to be put in place regardless). Alternatively if the substance has a high (>= 11.5) or low (=< 2) pH then testing for skin/eye irritation/sensitisation is not necessary since the substance is likely to be corrosive. If the substance is corrosive then there is also no need to conduct acute or repeat dose tests either. If existing data from a long term repeat dose toxicity test is available then short term repeat dose testing is not needed; conversely, if the compound is clearly identified as toxic or non-toxic in a shorter test then there is be limited information to be gained from conducting a longer test. Lack of dermal or oral absorption potential (or a characterized rate of absorption) can obviate further systemic testing by that exposure route (or enable hazard extrapolation).
  Information on effects on reproductive organs from repeated-dose studies, combined with negative developmental toxicity information, may obviate a traditional reproductive toxicity test
  http://www.epa.gov/hpv/pubs/general/sidsappb.pdf
  http://www.epa.gov/opptintr/chemrtk/
  Further guidance can be found in column 2 of the REACH annexes and the UK Health and Safety Executive 'minimization of animal use under REACH leaflet':
  http://www.icca-chem.org/en/Home/ICCA-initiatives/global-product-strategy/

- 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 49)

Gather Priority-relevant information

Table 5 below summarizes the hazard parameters or "endpoints" for which hazard information must be gathered based on the Priority 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. However a data gap is not always a data need. For example, within REACH it is accepted that if a substance is a genotoxic carcinogen then there is no need to test for reproductive toxicity (because appropriate risk measures need to be put in place regardless).

Table 5: Hazard "endpoints" for which information must be gathered according to Priorities

a) Human health

Priority 1 (High hazard and/or high exposure potential)	Priority 2 (Medium hazard and/or medium exposure potential)	Priority 3 (Low hazard and/or low exposure potential)	Priority 4 (Very low hazard and/or very low exposure potential)
Irritation (Eye / Skin) (e.g. in vitro test)	Irritation (Eye / Skin) (e.g. in vitro test)	Irritation (Eye / Skin) (e.g. in vitro test)	Irritation (Eye / Skin) in case of accidental exposure (e.g. in vitro test)
Mutagenicity (e.g. Ames, mammalian cell in vitro, in vivo micronucleus - only if positive in both in vitro tests)	Mutagenicity (e.g. Ames, mammalian cell in vitro, in vivo micronucleus - only if positive in both in vitro tests)	Mutagenicity (e.g. Ames test)	
Sensitization	Sensitization	Sensitization (required if triggered by structural alert)	
Repeated dose toxicity	Repeated dose toxicity		
Reproduction / developmental toxicity test			

STEP 4: DEVELOP PRIORITY-RELEVANT INFORMATION ("BASE SET OF INFORMATION")

b) Environment

Priority 1 (High hazard and/or high exposure potential)	Priority 2 (Medium hazard and/or medium exposure potential)	Priority 3 (Low hazard and/or low exposure potential)	Priority 4 (Very low hazard and/or very low exposure potential)
Acute toxicity to fish (e.g. short-term fish embryo test)	Acute toxicity to fish (e.g. short-term fish embryo test)	Acute toxicity to fish (e.g. short-term fish embryo test)	Acute toxicity to fish (e.g. short-term fish embryo test)
Acute Toxicity to Daphnia	Acute Toxicity to Daphnia	In case of accidental exposure relevant ecotoxicological data is needed	
Acute Toxicity to Algae	Acute Toxicity to Algae		
Chronic Toxicity (fish or daphnia) within limitations of the chemical properties			

Identify and fill information-gaps

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 acceptable and to be encouraged (see page 49). Where appropriate use non-animal methods first. 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.

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 has developed a GPS IT Portal that will provide its members with access to hazard information owned by companies http://www.icca-chem.org/en/Home/ICCA-initiatives/global-product-strategy/.

- **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 substances[17]**: Endpoint information for one chemical is used to make an endpoint prediction for another chemical, considered "similar" (e.g. OECD HPV program[18]). 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.

  For further information see:

  - OECD Guidance on Grouping of Chemicals http://www.oecd.org/officialdocuments/displaydocumentpdf?cote=env/jm/mono(2007)28&doclanguage=en.

  - The OECD QSAR Toolbox can be used to assist to identify chemicals which are similar to the target chemical http://www.oecd.org/env/existingchemicals/qsar.

  - 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).

STEP 4: DEVELOP PRIORITY-RELEVANT INFORMATION ("BASE SET OF INFORMATION")

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 70).

NOTE: However a data gap is not always a data need. For example, within REACH it is accepted that if a substance is a genotoxic carcinogen then there is no need to test for reproductive toxicity (because appropriate risk measures need to be put in place regardless). Alternatively if the substance has a high (>= 11.5) or low (=< 2) pH then testing for skin/eye irritation/sensitisation is not necessary since the substance is likely to be corrosive. If the substance is corrosive then there is also no need to conduct acute or repeat dose tests either. If existing data from a long term repeat dose toxicity test is available then short term repeat dose testing is not needed; conversely, if the compound is clearly identified as toxic or non-toxic in a shorter test then there is be limited information to be gained from conducting a longer test. Lack of dermal or oral absorption potential (or a characterized rate of absorption) can obviate further systemic testing by that exposure route (or enable hazard extrapolation). Information on effects on reproductive organs from repeated-dose studies, combined with negative developmental toxicity information, may obviate a traditional reproductive toxicity test (http://www.epa.gov/hpv/pubs/general/sidsappb.pdf) Further guidance can be found in column 2 of the REACH annexes and the UK Health and Safety Executive 'minimization of animal use under REACH leaflet': http://www.hse.gov.uk/reach/resources/18animaltesting.pdf

- *In vitro* methods
  Non-animal testing data generated using methods validated in accordance with internationally accepted principles (e.g. ECVAM, ICVAM, JCVAM, OECD). Increasing awareness of animal welfare has emphasized the need to reduce use of laboratory animals. The concept of the 3Rs was developed in 1959 with this in mind (Russell and Burch 1959). This states that efforts should be made to replace, reduce and refine the use of animals in experiments in the interests of sound science and animal welfare. General guidance for how to avoid unnecessary animal use when assessing the safety of chemicals can be found here:

  ECHA Practical guide 10 on how to avoid unnecessary testing on animals
  http://echa.europa.eu/doc/publications/practical_guides/pg_10_avoid_animal_testing_en.pdf

UK Health and Safety Executive 'minimization of animal use under REACH leaflet'
http://www.hse.gov.uk/reach/resources/18animaltesting.pdf

TSAR: Tracking System for Alternative test methods Review, Validation and Approval in the Context of EU Regulations on Chemicals http://tsar.jrc.ec.europa.eu/

- **(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 QSAR models has been accepted).

  REACH guidance on QSAR prediction models[19] can be found on:
  http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r6_en.pdf?vers=20_08_08

  ECHA Practical Guide 5 on how to report QSARs
  http://echa.europa.eu/doc/publications/practical_guides/pg_report_qsars.pdf

  OECD guidance on QSAR models and their validity[20] can be found on:
  http://www.oecd.org/document/2/0,3746,en_2649_34379_42926338_1_1_1_1,00.html

STEP 4: DEVELOP PRIORITY-RELEVANT INFORMATION ("BASE SET OF INFORMATION")

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/env/testguidelines
- International Conference of Harmonization (ICH) Guidelines
  http://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
- METI (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 Priority allocation)

- Developed further information, according to the Priority-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.

By assessing the exposures to a chemical first, one can better define the relevant hazard properties that need to be evaluated in addition. You have gathered existing information on the chemical for initial characterization of the hazard, and the exposure assessment will determine whether additional data is needed.

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

Following the initial GPS prioritization based on hazard criteria, the hazard characterisation will now proceed through a series of evaluation loops, beginning with a initial starting risk assessment, moving to levels of less uncertainty/increasing expertise, until a satisfactory conclusion can be reached. Every chemical needs to be assessed to the degree of certainty necessary to reach a sound risk management decision.

A chemical's potential to cause toxic or adverse effects is known as intrinsic hazard. Hazard Characterization is the process of determining if exposure (as calculated in chapter 5) 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 70 for more information on the hazard endpoints):

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

Weight of Evidence (WOE): The weight of evidence evaluation should include: the presence or absence of response in different taxa; the nature and magnitude of positive responses in relation to the relevance and reliability of the assays; dose response (or lack thereof); relative potency; and coherence of responses across assays in relation to the postulated mode of action.

In addition, in cases where the weight of evidence (derived from consideration of results of validated assays) indicates at most very low hazard potency and there is little or no likelihood of release to the environment or potential for exposure, then such substances should be given a very low priority for further investigation in definitive tests. Existing information and data from standard toxicity studies should be reviewed as part of the weight of evidence evaluation. Results from these studies can provide important information on dose response and adverse effects on endpoints of potential concern.

STEP 5: CHARACTERIZE HAZARD

Weight of Evidence approach considers:

- What endpoint has been measured and the relevance of that endpoint to the effects of potential endocrine disruption mechanisms (Data Relevance)

- The repeatability, reliability and quality of a particular study and its protocol, together with the extent of peer review (Study Repeatability)

- The significance (or "weight") of a data set based on the assessments (Data Significance)

- Whether there is sufficient coherence of the data to draw conclusions (balance of the "weight of evidence"), what further evidence is required to take action and what that action should be (Coherence, Gaps and Framework for Further Action)

- Expert judgment is required at each stage and it is important to record the basis of decisions to aid transparency

- More guidance can be found under: http://www.biac.org/statements/chem/FIN08-12_BIAC_Perspective_on_a_Globally_Harmonized_Endocrine_Activity_Assessment_Approach.pdf

Human Health End Points	Environmental End Points
1. Acute toxicity 2. Irritation and Corrosivity 3. Sensitization 4. Mutagenicity and Genotoxicity 5. Repeated Dose toxicity 6. Reproductive / Developmental toxicity	1. Aquatic toxicity 2. Degradation, bioaccumulation

Prior to embarking on Step 5, it is important to take into account the considerations below. The Supplement starting on page 70 gives more detail should you need it.

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.

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 ld 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 a chemical, or its active metabolite, reaches a threshold concentration in the relevant organ but this is only valid for non-cancer endpoints. 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 96).
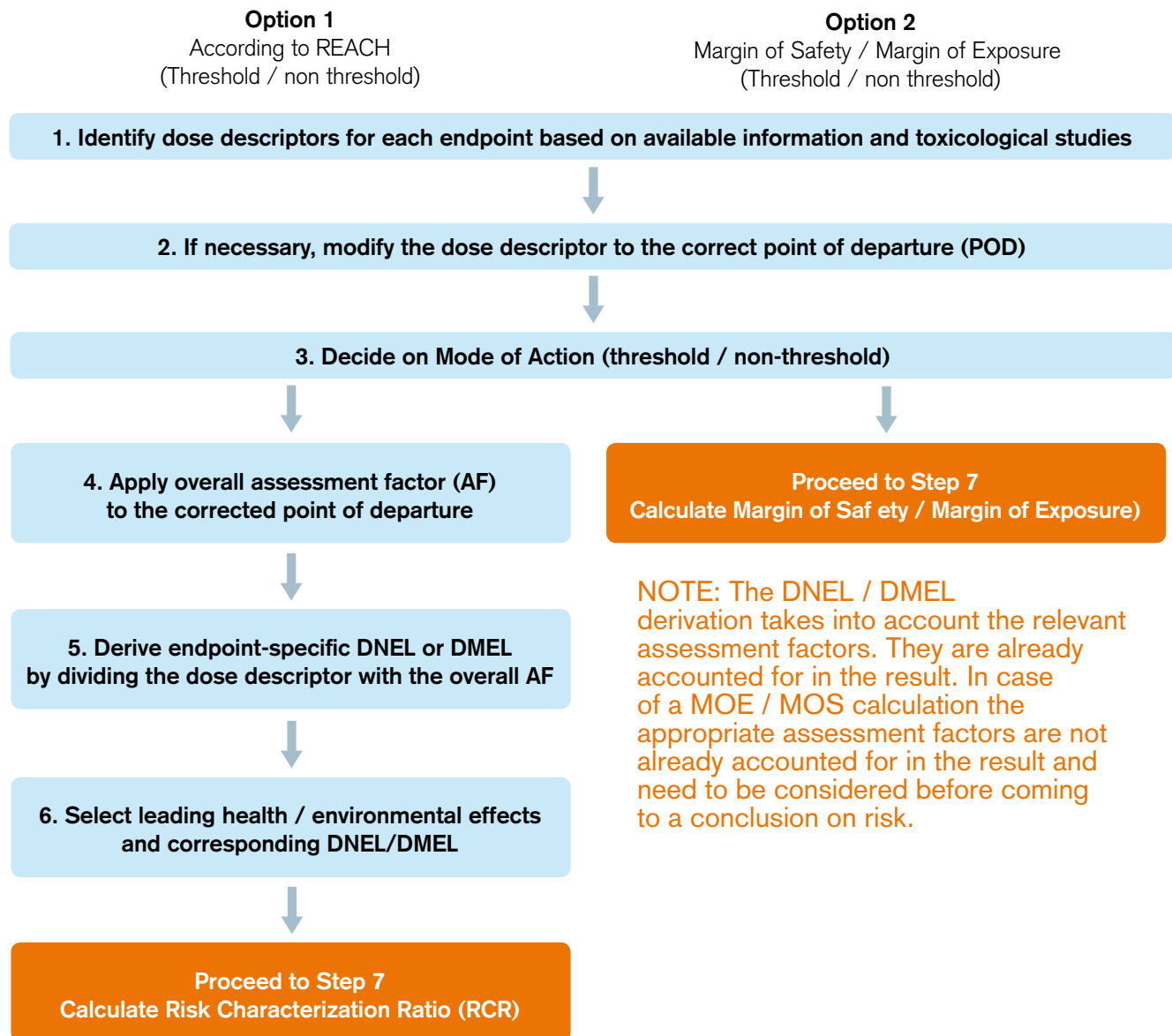
./...

STEP 5: CHARACTERIZE HAZARD

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 138).

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 95).

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 101 for a worked through DNEL calculation.

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

Option 1
According to REACH
(Threshold / non threshold)

Option 2
Margin of Safety / Margin of Exposure
(Threshold / non threshold)

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

↓

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

↓

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

↓ ↓

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

Proceed to Step 7 Calculate Margin of Safety / Margin of Exposure)

↓

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

NOTE: The DNEL / DMEL derivation takes into account the relevant assessment factors. They are already accounted for in the result. In case of a MOE / MOS calculation the appropriate assessment factors are not already accounted for in the result and need to be considered before coming to a conclusion on risk.

↓

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

↓

Proceed to Step 7 Calculate Risk Characterization Ratio (RCR)

STEP 5: CHARACTERIZE HAZARD

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 133.

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 95 for more information on dose descriptors and page 70 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.

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 133) 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)

Every risk assessment needs a point of departure (POD). This can either be the NOAEL ("no observed adverse effect level") or the Benchmark dose (BMD) and its lower confidence limit (BMDL). In most cases you can use the values identified in the animal study directly and calculate the corresponding human threshold level by applying appropriate assessment factors (AF). In some cases however the identified NOAEL or BMD needs to be slightly adjusted for e.g. know differences in breathing rates, longer exposure durations, differences in metabolic rates between animals and humans. For example, assume that NOAEL you've identified in an inhalation study is 1,000 mg. In this study the animals are usually resting in the experimental setups where they are exposed. Now if you want to use this value for an assessment of workers which are physically active and have to lift heavy weights they will have a higher breathing rate than the animals in the study. Therefore they will take up much more air (and be exposed at a higher level). Therefore you should multiply the NOAEL of 1000mg with 0.75 to adjust the POD for the differences between human / animal.

STEP 5: CHARACTERIZE HAZARD

However as the AF used in the subsequent assessment are usually very conservative, the threshold levels in most cases will still provide sufficient margin of safety even without POD adjustment.

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 Facto*r is used for a numerical value, which covers both dose adjustment and data uncertainty.

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.

./...

STEP 5: CHARACTERIZE HAZARD

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.

Industry Perspective on Assessment Factors
Since the publication of the REACH assessment factor guidance (chapter R.8 of the Guidance on information requirements and chemical safety assessment) chemical companies have been preparing and submitting registrations. Thereby, valuable experience has been gained on deriving DNEL using the R.8 guidance and on balancing these with the exposure predictions using the ECETOC targeted risk assessment (TRA) tools and other models. It is becoming clear that even for relatively data-rich chemicals submitted in the first tier of registrations (by December 2010) the multiplication of AF result in DNELs that are relatively low. These DNELs are sometimes difficult to balance with the conservative exposure predictions, derived using screening tools such as the ECETOC TRA. This may especially be the case, if the compounding of individual AF leads to unnecessary conservatism that can justifiably be avoided.

It is generally recognized that the use of informed AF is preferred over default AF wherever possible, whether supported by substance-specific data or, for example, by read-across to other chemicals or mechanisms of action. The use of informed AF for hazard and risk assessment is well-established and has been used for many years by organizations such as the Scientific Committee on Occupational Exposure Limits (SCOEL) and national competent authorities to set occupational exposure limits.

ECETOC, the European Centre for Ecotoxicology and Toxicology of Chemicals, reviewed in 2003 and 2010 the ECHA assessment factors based upon an extensive and documented scientific review of the available literature. If substance or category specific information, such as route specific absorption rate, is available, there may be scientific justification of deviating from the ECHA default assessment factors to predict the effects in humans.

For the ECHA and ECETOC Assessment Factor Tables please refer to pages 98-100.

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 104.

(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.

STEP 5: CHARACTERIZE HAZARD

This will be a case to case decision and depend on expert judgment.

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

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.

DMEL Derivation (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 136.

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 132).

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). PNEC derivation is based on the lowest EC50 or NOEC of the dataset for each compartment.

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 organisms[23]. 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.

PNEC = L(E)C50 / AFs

STEP 5: CHARACTERIZE HAZARD

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 are not necessarily from the most sensitive species (applied to the species lowest NOEC)	50
Chronic toxicity data based on 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.

For more information see Chapter R10 of ECHA guidance document on information requirements and chemical safety report.
http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r10_en.pdf?vers=20_08_0

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) modelling[24], (ii) *in vitro* studies and (iii) *in vivo* studies. However, animal testing (in vivo studies) should be conducted only as a last resort and all reasonable attempts be made to obtain the required information by other means. Some good examples are provided in UK Health and Safety Executive "minimization of animal use under REACH leaflet".
http://www.hse.gov.uk/reach/resources/18animaltesting.pdf

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.

- OECD (Q)SAR Toolbox (continually expanding, currently covers bioaccumulation, fish toxicity, skin sensitization, skin/eye irritation, mutagenicity-training materials and opportunities offered).
  http://www.oecd.org/document/54/0,3746,
  en_2649_34379_42923638_1_1_1_1,00.html

- EU list of QSAR models (DART for setting assessment priorities, Toxmatch for grouping and read-across, Toxtree for ecotoxicity and toxicity predictions, and CRAFT and METIS for metabolism and fate prediction).
  http://ihcp.jrc.ec.europa.eu/our_labs/computational_toxicology

- INCHEMICOTOX, quality assured databases together with Integrated Testing Strategies decisions tools for skin sensitisation and aquatic acute toxicity are available. http://www.inchemicotox.org/

- CAESAR http://www.caesar-project.eu
  A series of statistically-based models, implemented into open-source software and made available for online use via the web. Predictions are made for five endpoints: mutagenicity (Ames), carcinogenicity, developmental toxicity, skin sensitisation, and the bioconcentration factor.

- Lazar http://lazar.in-silico.de/ is an open-source software programme that makes predictions of toxicological endpoints (currently, mutagenicity, human liver toxicity, rodent and hamster carcinogenicity).

- ORCHESTRA http://www.orchestra-qsar.eu/
  This is a project for disseminating and exploiting the activities of ongoing EU research concerning in silico (QSAR, read-across, etc.) models for the (eco)toxicology.

- T.E.S.T. Toxicity estimation software tool[25] (download software and training tools here: www.epa.gov/nrmrl/std/cppb/qsar/index.html#TEST)

- MultiCase[26] (commercial QSAR regression model that uses fragments and statistical rules to identify active and inactive fragments www.multicase.com/)

- DEREK[27] (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.

- TOPKAT[28] (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

- HazardExpert[29] (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 metabolites[30]. 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 Endpoints

1. Acute toxicity

Assessing the acute toxicity potential of all chemicals from Priority 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 NOAEL in single administration studies). In addition human data and experience as being a source of information on acute toxicity.

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 73):

(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 assay[31] (http://iccvam.niehs.nih.gov/methods/acutetox/inv_nru_brd.htm).

- Trans-epithelial resistance (TER), coupled with enhanced paracellular permeability (PCP)

- TSAR: Tracking System for Alternative test methods Review, Validation and Approval in the Context of EU Regulations on Chemicals http://tsar.jrc.ec.europa.eu/

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

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

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 (pH $\leq$ 2 and $\geq$ 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 73). Or alternatively the OECD QSAR Toolbox http://www.oecd.org/document /54/0,3746,en_2649_34379_42923638_1_1_1_1,00.html

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

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

(iii) *In vivo* **methods:** The classic skin and eye irritation test was the rabbit (Draize) test. To reduce and refine unnecesarry testing for animal welfare reasons the OECD and ECVAM have now approved in vitro and ex vivo method for both skin and eye irritation. These can be used as a standalone to replace the rabbit or used together with the in vitro method above in a testing strategy to capture irritation.

However, when evaluating existing studies 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	**404** Acute Dermal Irritation / Corrosion **405** Acute Eye Irritation / Corrosion	**870.2400** Acute Eye Irritation **870.2500** Acute Dermal Irritation	**10993-3** Biological evaluation of medical devices - Part 10: Test for irritation and sensitization

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) can provide information on the dose response relationship. 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). Approaches are also available for conducting quantitative risk assessments that consider the identification of a predicted threshold dose for sensitization (referred to as the no expected sensitization induction level (NESIL)) that considers application of safety factors to derive an acceptable exposure level (Cite Api et al., 2008 and Loveless et al., 2010). Sometimes even NOAEL values might be available from historical human data (see REACH Rip. R8, Appendix R8-10). If a quantitative risk assessment cannot be developed, 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 73).
Or alternatively the OECD QSAR Toolbox http://www.oecd.org/document/54/0,3746, en_2649_34379_42923638_1_1_1_1,00.html

(ii) *In vitro* **methods:** There are no officially adopted in vitro tests for skin or respiratory sensitization. You can check for updates under the following weblink:
TSAR: Tracking System for Alternative test methods Review, Validation and Approval in the Context of EU Regulations on Chemicals http://tsar.jrc.ec.europa.eu/

(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. The LLNA should therefore be used in prefer ence to the guinea pig (TG 406) for both scientific and animal welfare reasons. The OECD have recently revised TG429 to include a reduced test, using fewer animals that can be used when information on potency is not required.

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)[32].

The standard test for mutageniciy 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 Priority stages (Priority 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. Further guidance on testing schemes and test hierachy is avaialble via the endpoint specific guidance within the REACH Rip. R7a, page 395.

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. Or alternatively the OECD QSAR Toolbox http://www.oecd.org/document/23/0,3343,en_2649_34379_33957015_1_1_1_1,00.html

(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	**471** Bacterial Reverse Mutation Test **472** Genetic Toxicology: Escherichia coli, Reverse Assay **473** In Vitro Mammalian Chromosome Aberration Test **476** In Vitro Mammalian Cell Gene Mutation **479** Genetic Toxicology: In Vitro Sister Chromatid Exchange assay **480** Genetic Toxicology: Saccharomyces cerevisiae, Gene Mutation Assay **481** Genetic Toxicology: Saccharomyces cerevisiae, Mitotic Recombination Assay **482** Genetic Toxicology: DNA Damage and Repair, Unscheduled DNA Synthesis in Mammalian Cells In Vitro **487** In Vitro Mammalian Cell Micronucleus Test	**870.5100** Bacterial Reverse Mutation Test **870.5140** Gene Mutation in Aspergillus nidulans **870.5300** In vitro Mammalian Cell Gene Mutation Test **870.5375** In Vitro Mammalian Chromosome Aberration Test **870.5500** Bacterial DNA Damage or Repair Tests **870.5550** Unscheduled DNA Synthesis in Mammalian Cells in Culture **870.5575** Mitotic Gene Conversion in Saccharomyces cerevisiae **870.5900** In Vitro Sister Chromatid Exchange Assay **870.5915** In Vitro Sister Chromatid Exchange Assay

(iii) **In vivo** **methods:** In vitro methods should be employed first. Only in the scenario where a positive result is found in the in vitro test should a follow up in vivo test be considered. Regulalatory requirements however always have precedence.

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

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. Priority 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.

In certain cases also animal studies primarily focusing on reproductive and/or developmental toxicity parameters may provide some additional information on general toxicological effects arising from repeated exposures of the parental generation. Such information should also be taken into account. 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 bw/d 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	**407** Repeated Dose 28-Day Oral Toxicity Study in Rodents	**870.3050** Repeated Dose 28-day Oral Toxicity Study in Rodents
	408 Repeated Dose 90-Day Oral Toxicity Study in Rodents	**870.3100** 90-Day Oral Toxicity in Rodents
	409 Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents	**870.3150** 90-Day Oral Toxicity in Nonrodents
	410 Repeated Dose Dermal Toxicity: 21/28-day	**870.3200** 21/28-Day Dermal Toxicity
	411 Subchronic dermal Toxicity: 90-Day	**870.3250** 90-Day Dermal Toxicity
	412 Sub acute Inhalation Toxicity: 14/28- Day Study	**870.3465** 90-Day Inhalation Toxicity
	413 Subchronic Inhalation Toxicity: 90-Day Study	**870.3650** Combined Repeated Dose Toxicity with the Reproduction/Development Toxicity Screening Test
	422 Combined Repeated Dose Toxicity Study with the Reproduction /Developmental Toxicity Screening Test	**870.4100** Chronic Toxicity
	452 Chronic Toxicity Studies	**870.4300** Combined Chronic Toxicity / Carcinogenicity

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 Priority 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 were appropriate testing has been conducted at dose levels up to the maximum required under the standard test guidelines 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 substance[33]. 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 test[34]

• Limb bud micromass culture[35]

• Whole embryo culture[36]

(iii) *In vivo* methods:

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

Environmental Hazard Endpoints

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.

- The Ecological Structure Activity Relationships (ECOSAR) Class Program from the US-EPA is a computerized predictive system that estimates the aquatic toxicity of industrial chemicals.
  The program estimates a chemical's acute (short-term) toxicity and chronic (long-term or delayed) toxicity to aquatic organisms such as fish, aquatic invertebrates, and aquatic plants by using Structure Activity Relationships (SARs). http://www.epa.gov/opptintr/newchems/tools/21ecosar.htm

- OECD QSAR 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 categories[37]. http://www.oecd.org/document/23/0,3343, en_2649_34379_33957015_1_1_1_1,00.html

- TSAR: Tracking System for Alternative test methods Review, Validation and Approval in the Context of EU Regulations on Chemicals. http://tsar.jrc.ec.europa.eu/

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

(iii) **_in vivo_ methods:**

Hazard	OECD	US EPA	ISO
Acute	**126** Short Guidance on the Threshold approach for Acute Fish Toxicity **201** Alga, Growth Inhibition **202** Daphnia sp. Acute immobilisation Test **203** Fish, Acute Toxicity **209** Activated Sludge, Respiration Inhibition **221** Lemna sp. Growth Inhibition Test	**850.1010** Invetebrate Acute Toxicity **850.1020** Gammarid Acute **850.1025** Oyster Acute **850.1035** Mysid Acute T **850.1045** Penaeid Acute **850.1055** Bivalve Acute **850.1075** Fish Acute **850.1085** Fish Acute	**8692** Fresh water algal growth inhibition **6341** Acute toxicity test **7346 -1,-2,-3** Acute lethal toxicity freshwater fish **20079** Duckweed growth inhibition test
Chronic	**204** Fish, Prolonged Toxicity Test: 14-Day Study **210** Fish, Early-Life Stage **211** Daphnia magna Reproduction **212** Fish, Short- term Toxicity Test **215** Fish, Juvenile Growth **229** Fish Short Term Reproduction Assay **230** 21-Day Fish Assay: A Short Term Screening for Oestrogenic and Androgenic Activity, and Aromatase Inhibition **231** Amphibian Metamorphosis Assay	**850.1300** Daphnid Chronic Toxicity Test **850.1350** Mysid Chronic Toxicity Test **850.1400** Fish Early-Life Stage Toxicity Test **850.1500** Fish Life Cycle Toxicity	**10229** Prolonged toxicity of substances to freshwater fish **10706** Determination of long term toxicity to Daphnia magna Straus **12890** Embryo-larval toxicity to freshwater fish

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 Priority 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 (Kow) 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. Kow does not need to be determined if the substance is purely inorganic. Kow 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. Kow 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 Kow.

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 ecosystems[38]. 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 *Or not readily or inherently biodegradable* *Or predicted biodegradability in a time frame of weeks-months*	Half-life > 60 d in marine or freshwater or > 180 d in marine or freshwater sediment *Or not readily or inherently biodegradable* *Or predicted biodegradability in a time frame of weeks-months*
B	BCF > 2,000 Or log Kow > 4.5	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 data[39].

(i) **Modeling:** It may be possible to avoid conducting the BCF test on fish through use of these models.

• BCFBAF™ (EPI Suite, EPA web site): Formerly called BCFWIN™, Syracuse Research Corporation, Bioconcentration Factor Program (BCFWIN), Version 2.15. downloadable at http://www.epa.gov/oppt/exposure/pubs/episuite.htm

• European Commission Review of QSAR models for Bioconcentration factor (2006) http://ecb.jrc.ec.europa.eu/documents/QSAR/QSAR_Review_Bioconcentration.pdf

• CATALOGIC (formerly CATABOL) is also appropriate: the model predict persistency, biodegradation, etc. Predicts the magnitude and physicochemical and toxic endpoints of stable degradants across biodegradation pathways of the chemicals. http://oasis-lmc.org/?section=software&swid=1

(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	CO_2 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 on Assessment Factors

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

Table 10: ECETOC Informed Assessment Factors

	Rational	Systemic effects	Local effects
Interspecies	• Correction for differences in metabolic rate (allometric factor) • "remaining differences"	4 (rat → humans) 7 (mice → humans) n.a.; in allometry factor	1 1
Intraspecies	• Worker • General population	3 5	3 5
Time extrapolation	• Sub-acute to sub-chronic • Sub-chronic to chronic • Sub-acute to chronic	3 2 6	1 1 1
Route to route extrapolation	• Oral to inhalation • Dermal to inhalation	*	n.a.
Dose-response/ severity of effect	• Reliability of the dose-response, LOAEL/NOAEL extrapolation and severity of effect	3	*
Quality of whole data base	• Completeness and consistency of the available data • Reliability of alternative data (e.g. read across)	*	*

n.a. = not applicable
* no recommendation by ECETOC (i.e. ≥1)

Human Data

In case of human data ECETOC presented typical assessment factors. In contrast to data generated on experimental animals, data on human exposure and effects are less controlled and therefore require greater expert interpretation. The recommended assessment factors are typical maximum values that may be considered appropriate on a case-by-case basis to account for study deficiencies and are not intended to be arbitrarily multiplied together.

Table 11: ECETOC Typical Assessment Factors Applied to Human Data

	Nature of assessment factor	AF* applied to account for deficiency
Intraspecies	• Worker to worker	1
	• Worker to general population	2
	• General population to general population	1
Time extrapolation	• Sub/semi-chronic to chronic	2
	• Chronic to lifetime	1
Dose-response	• LOAEL/NOAEL extrapolation	2**
	• Steep dose-response curve	2
Quality of whole data base	• Issues related to completeness of available data	***
	• Issues related to consistencty of available data	****
	• Issues related to reliability of available data	2
	• Study substantiality influenced by healthy worker effect	2
	• Small study size	3

*   AF is typical factor applied rather than default for all situations.

**   Typically a value of 2 is sufficient, but if information on the dose-response curve is available a more appropriate AF should be used.

*** No general AF can be recommended; expert judgement is required on a case-by-case basis.

**** No general AF can be recommended; if the human data are inconsistent, refer to animal data.

Reference/further information:

- ECETOC (2010). Guidance on Assessment Factors to Derive a DNEL. Technical Report No. 110. Brussels.
- ECETOC (2003). Derivation of Assessment Factors for Human Health Risk Assessment. Technical Report No. 86. Brussels.
- ECETOC (2009). Framework for the Integration of Human and Animal Data in Chemical Risk Assessment. Technical Report No. 104. Brussels.

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

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

Developmental Systemic) Effects
- Substance-specific data indicates dermal absorption is 2x less in humans than rats

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

Step 4: Apply Assessment Factors

	Irritation	Adrenal effects	Developmental effects
(modified) NOAEL	50	20	100
Intraspecies	5	5	5
Interspecies	1	10	10
Duration	2	2	2
Dose-Responce	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 r oute 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
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 10 = 50**
DMEL ppm/kg/bw/d	**0.5 ppm**

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 agent[40]. 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.

Potential for exposure can differ from company to company, product to product and country to country. The production of a chemical can for example be based on different processes – the risk minimisation measures in place at the workspace such as ventilation systems or personal protection equipment can differ – the concentrations in the end product can be specific to a companies use / application of the chemical. There are many factors specific to production / handling / use and recycling of products which lead to differences in exposure levels. They need to be assessed and accounted for in each case of the risk assessment.

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 detailed on page 107.

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 on the following page 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.

STEP 6: ASSESS EXPOSURE

Figure 4: The life cycle of a chemical
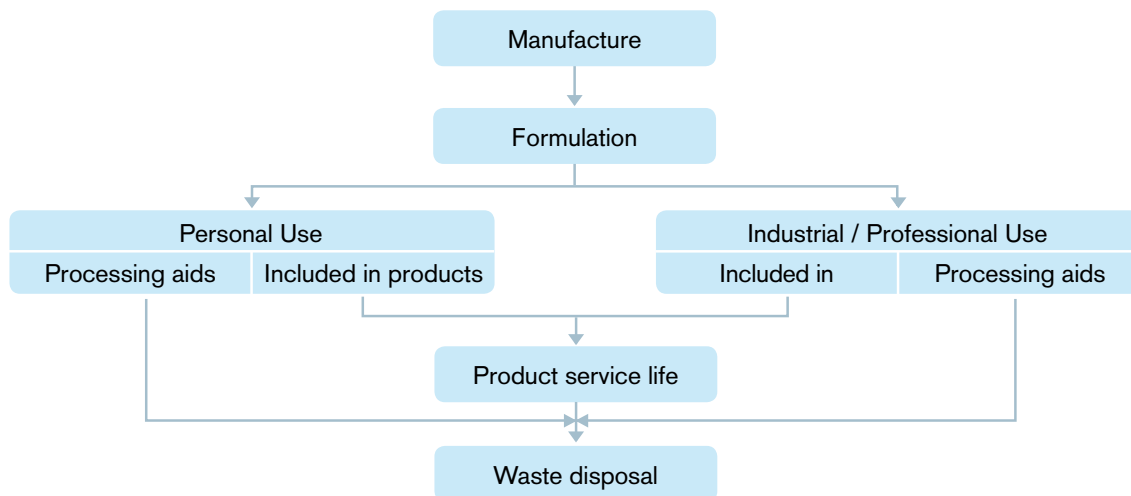
4. **Consider exposure to workers, consumers and the environment:**
   Workers may be exposed to chemicals in the workplace. In general, workers are a more homogenous group than consumers – but their potential exposures are likely to be greater. A consumer product is a product that can be purchased from 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 18). The table below summarizes the relevant determinants required in order to conduct an exposure assessment:

Table 12: 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 19).

Table 13: 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	

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*
    GPS in general applies to chemicals in commerce. Intermediates are consumed in the subsequent chemical processing and therefore no exposure to the general public is to be expected. Transported intermediates however are within the scope of GPS as they leave the facility site and potential for exposure increases e.g. accidents. On-site or non-isolated intermediates are not part of the GPS scope.

    Intermediates are 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.

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 use[41]
  http://ec.europa.eu/environment/emas/pdf/general/nacecodes_en.pdf

- Japanese Use Category under amended CSCL
  http://www.meti.go.jp/policy/chemical_management/english/cscl.html

- OECD Use patterns (Main Pattern, Industrial and Use Category)[42]
  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 122)

- 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 122). 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.

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 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 characteristics (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 124 of the Supplement.

The preferred tool (ECETOC TRA) is described in the supplement from page 127. A template with drop down menus for collection of Tier 1 information for ECETOC TRA can be downloaded from Cefic website:
http://www.cefic.org/Industry-support/Responsible-Care-tools-SMEs/Product-stewardship/Cefic-Guidances-to-Implement-the-Global-Product-Strategy-GPS/

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 AC, 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 and commercial products 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). Those should be given preference whenever possible without losing function / benefits. Where RMMs take the form of consumer instructions (e.g. wear gloves, do not use without sufficient ventilation) a sufficient degree of implementation needs to be assumed. Packaging instructions need to be simple and specific.

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 page 123) as well as intended or foreseeable use. Examples of exposure estimation models are provided on page 124 in the Supplement.

Based on experience with the REACH registration the preferred tool (ECETOC TRA) is described in the Supplement from page 127. A template with drop down menus for collection of Tier 1 information for ECETOC TRA can be downloaded from Cefic website: http://www.cefic.org/Industry-support/Responsible-Care-tools-SMEs/Product-stewardship/Cefic-Guidances-to-Implement-the-Global-Product-Strategy-GPS/

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 aadequate 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

STEP 6: ASSESS EXPOSURE

Tools to Calculate Exposure

The preferred tool (ECETOC TRA) is described from page 127 in Supplement.
A template with drop down menus for collection of Tier 1 information for Ecetoc TRA
can be downloaded from Cefic website:
http://www.cefic.org/Industry-support/Responsible-Care-tools-SMEs/Product-stewardship/Cefic-Guidances-to-Implement-the-Global-Product-Strategy-GPS/

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://www.cefic.org/Industry-support/Responsible-Care-tools-SMEs/Product-stewardship/Cefic-Guidances-to-Implement-the-Global-Product-Strategy-GPS/

In addition, for PEC exposure calculations on some of the above targets, the EUSES
modeling programs (http://ihcp.jrc.ec.europa.eu/our_activities/health-env/risk_assessment_of_Biocides/euses) and EU-TGD-Spreadsheets (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 14: 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 15: 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 16: Environmental Release Estimation Models

Environmental Release Estimation Models (for web link see glossary)
EUSES http://ihcp.jrc.ec.europa.eu/our_activities/health-env/risk_assessment_of_Biocides/euses EU TGD http://ihcp.jrc.ec.europa.eu/our_activities/health-env/risk_assessment_of_Biocides/doc/tgd Higher Priority models have been developed Overview from: http://focus.jrc.ec.europa.eu

Table 17: 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 UseR	http://www.cefic.org/Industry-support/Responsible-Care-tools-SMEs/Product-stewardship/Cefic-Guidances-to-Implement-the-Global-Product-Strategy-GPS/
ECETOC TRA	See chapter below
Emission scenario documents published by OECD	http://www.oecd.org/env/riskassessment
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 Priority 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://www.cefic.org/Industry-support/Implementing-reach/Libraries/

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 TRA[43] (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

Basic information (essential)

Step 1 — Identification of the substance

Input data
- Substance name
- CAS No.
- Sector Use (SU)

Step 2 — Physio-chemical properties

- Molecular weight
- Vapor pressure
- Partition coefficient (Kow)
- Biodegradability
- Water solubility
- Koc

Select and execute Step 3a, Step 3b, or Step 3c based on exposure scenarios

Step 3a
- PROC
- OC
- RMM
- DNEL

Risk assessment for occupational exposure
- Estimated exposure
- Risk characterization ratio

Step 3b
- PC
- AC
- DNEL

Risk assessment for consumer exposure
- Estimated exposure
- Risk characterization ratio

Step 3c
- ERC
- PNEC

Risk assessment for environmental exposure
- Estimated exposure
- Risk characterization ratio

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 bw/d

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/d 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.

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.

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:

$$RCR = EXPOSURE / DNEL$$

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 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.

$$RCR = EXPOSURE / DMEL$$

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.

$$RCR = PEC / PNEC$$

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

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)OAEL, 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)OAEL 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:

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

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 143 for a worked through MOS example, and page 145 for MOE.

DNEL versus Margin of Safety (MOS)

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

If MOS > Overall Assessment Factor → No concern
If MOS < Overall Assessment Factor → Concern

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

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.

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 assessment[44] (http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_part_d_en.pdf)

• CEFIC library for RMMs[45] 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.

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 BDI[46] 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 ≥ 1: Risk is high: detailed assessment and risk reduction measures required

- Long term dermal exposure systemic

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

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 bw/day (approximate mean value). This value is approximately 7 times lower than the NOAEL of 0.5 mg/kg bw/day for neuropathological effects and about 30 times lower than the LOAEL of 2 mg/kg bw/day for the slight neuropathological effects that were observed in an animal study.

Effect	Estimated total exposure (mg/kg bw/d)	NOAEL (mg/kg bw/d)	LOAEL (mg/kg bw/d)	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 $0.0007 + 5.10{-}5 = 0.001$ mg/kg bw/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 bw/d)	NOAEL (mg/kg bw/d)	LOAEL (mg/kg bw/d)	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 bw/d)	Exposure Dose (mg/kg bw/d) *(Source of Value)*	Calculation	MOE	Potential for Risk?
Worker	Dev. Tox	10	**0.599** *(ChemSTEER APDR, Inhalation)*	$\dfrac{10}{0.599}$	16.7	Yes
General Pop.	Dev. Tox	10	**8.13x10-2** *(E-FAST ADRpot, Fish Ingestion)*	$\dfrac{10}{8.13\text{x}10\text{-}2}$	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.

STEP 8: DOCUMENT OUTCOMES

Document 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. A GPS safety summary is not a legal document and not intented to replace legal documents such as the MSDS. It is the result of a voluntary commitment made by industry as a contribution to the SAICM goal. The GPS Safety Summary is intended to provide a general overview of the major characteristics of the chemical substance, include a short overview of the outcome of the chemical risk assessment and to transparently provide access to information in suitable format to increase public confidence that chemicals are safely handled throughout their life cycle. The summary should be fairly basic and understood by a layman, therefore the use of technical terminology is minimized in favor of general terms. It is not intended to replace legal communication documents such as the eSDS – 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.

STEP 8: DOCUMENT OUTCOMES

Safety summaries are to be prepared ideally as a joint effort of the risk assessment expert, the business units and if possible a company communicator who will polish and simplify the language for public use. Companies may sub-contract the preparation of the safety summaries, but publication will always be under company responsibility. In case a chemical is produced by other companies as well, we encourage companies to work in consortia to produce joint Safety Summaries. This will not only reduce the workload for each company and avoid unnecessary duplications while at the same time ensures that companies do not publish conflicting information on the same substance.

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

ICCA does not mandate a specific format or content for a safety summary. Companies are free to prepare the safety summary in their own format. For those companies that prefer some guidance, the ICCA guidance on risk assessment gives information on what could be in the safety summary. The content described should be seen as best practice recommendation, companies are welcome to develop their own format, but each company is responsible for the validity of the information provided. The GPS safety summaries should be frequently reviewed and updated to incorporate changes or new information. In addition Cefic has published a template for conversion of a REACH dossier, but the template could also be used where there is no REACH dossier: http://www.cefic.org/Industry-support/Implementing-reach/Documents-and-Tools1/

The list below captures some of the elements than can be incorporated into the GPS Safety Summary. For a template refer to pages 150-153.

- 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 summaries[47] currently available for each company on this page http://reporting.responsiblecare-us.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	✓		

	Extended HPV Challenge Work	Inventory Update Rule Report	REACH Chemical Safety Report	Work in reviewing for GHS compliance	Food Contact Notification	Pesticide applications

ADDENDUM 1

Assessing Toxicity of Mixtures (Preparations and Formulations)

The main section of the GPS guidance outlines the principles of the risk assessment of a single chemical. Chemical manufactures produce and sell in addition to single chemical compounds formulations and / or preparations of multiple substances. For the majority of formulations, toxicity is determined by the toxicity of one chemical or several chemicals acting independently. This occurs because the toxicities of the components vary from one component to the next and because the concentrations of the components in a formulation also vary. There is however some in-vivo evidence, that chemicals, which have the same mode of action (MoA) or the same target organ can also show dose additivity for common effects. However, there is little or no in-vivo evidence for a dose additivity of chemicals with dissimilar modes of actions. Current substance based risk assessment methods are still considered to be protective in the majority of cases.

NOTE: Mixture in the context of the GPS risk assessment refers to a preparation (or formulation) sold into commerce that is composed of two or more chemical substances (and their impurities) and will result in simultaneous exposures of the substances to an individual. Substance means a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve the stability and impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition.

Additives are additional substances that have been intentionally added to stabilize the substance which contributes to the substance composition (but not to the naming).

Impurities are unintended constituents present in a substance, as produced that does not contribute to the naming of the substance. Identification and quantification of impurities is required for all impurities (including isomers and by-products) if above 1% and those impurities from 0.1% onwards that are relevant for the hazard classification and/or PBT assessment.

Risk Assessment Approaches

Currently, there is no single universally accepted methodology for the assessment of the risks posed by mixtures. The ICCA GPS guidance will reflect different approaches to quantitative risk assessment of a chemical mixture, the choice depending upon the type of available test data and the information on mode of action of the single components. The following scenarios might apply when looking at data availability:

In the first situation, direct toxicity data on the mixture itself might be available; in this case the quantitative risk assessment is done directly from these preferred data, following the same processes as outlined in the guidance for single substance assessment. However, please keep in mind that the assessment is only valid as long as the composition and the concentrations of the components of the mixture are not changed. In certain cases it is also possible to draw conclusions from available data of similar mixtures. This might especially be the case for some human health endpoints, such as skin irritation, were information frequently is available from testing the mixture itself. In these cases, the toxicity data from the whole mixture should be used to identify suitable risk management measures.

In the second situation, no actual data on the mixture as such is available; the mixture toxicity is evaluated through an analysis of its individual components. For component-based risk assessment, information on mode or mechanism of action will determine which mixtures additivity method to apply (independent action versus dose addition).

Up to now there is no harmonized globally accepted methodology for a risk assessment of a mixture but science is evolving fast and there are a number of national / regional and sector-specific (e.g. pesticides) mixture risk assessment methods in use (Meek et al. 2011; USEPA 2007; IGHRC 2007; USEPA 2000). The selection of the subsequent assessment method still depends on data availability and quality.

For more information please refer to:

- Meek, M.E.(Bette), Boobis, A.R., Crofton, K.M., Heinemeyer, G., Raaij, M.V., Vickers, C., Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework, Regulatory Toxicology and Pharmacology (2011), doi: 10.1016/j.yrtph.2011.03.010

- U.S. EPA. Concepts, methods and data sources for cumulative health risk assessment of multiple chemicals, exposures and effects: A resource document. Cincinnati, OH: U.S. EnvironmentalProtection Agency, Office of Research and Development, National Center for Environmental Assessment, 2007. (EPA/600/R-06/013F)

ADDENDUM 1
Assessing Toxicity of Mixtures

- Interdepartmental Group on Health Risks from Chemicals (IGHRC). Chemical mixtures: A framework for assessing risks (Version 6, April 2007) Available at: http://ieh.cranfield.ac.uk/ighrc/mixtures_document.pdf

- Agency for Toxic Substances and Disease Registry (ATSDR). Guidance Manual for the Assessment of Joint Toxic Actions of Chemical Mixtures. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, 2004

- U.S. EPA. Supplementary guidance for conducting health risk assessment of chemical mixtures. In: Risk Assessment Forum, Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development, 2000. (EPA 630/R-00-002)

- IPCS, 2001, "Integrated risk assessment report, Report prepared for WHO/UNEP/ILO", International Program on Chemical Safety, World Health Organization. Available: http://www.who.int/ipcs/publications/new_issues/ira/en/index.html

Methods / Tools to assess mixture toxicity

1. Hazard Index (HI)

A simple method for component-based risk assessment of toxicologically similar chemicals is the Hazard Index (however not applicable for non-threshold / genotoxic carcinogenic mode of action as it is not possible to define a safe threshold level for those chemicals). The HI per substance is calculated by dividing the concentration of chemical in the mixture by the concentration limit for chemical that was still assessed to be safe (e.g. the DNEL value derived in the single substance assessment).

$$HI = \frac{\text{Exposure level}}{\text{Threshold level of the substance (e.g. DNEL, PNEC, ADI)}}$$

HI (mixture) = HI (substance 1) + HI (Substance 2) + etc.

As long as the resulting HI value is < 1 the limit for that single chemical has not been exceeded (you will notice the similarities to the REACH single substance Risk Characterization Ratio i.e. RCR approach). However, if the hazard indices for all chemicals in a mixture are added together and the cumulative HI is > than 1, then an unacceptable condition may exist and mitigating strategies may need to be considered.

The HI is a simple straight forward approach but influenced / affected by the assessment factors used to calculate the respective DNELs, PNECs and ADI values.

For more information please refer to:

- NCEA Scientific Review on Guidance for Conducting Health Risk Assessment of Chemical Mixtures available via http://www.epa.gov/ncea/pdfs/mixtures.pdf

- Gutierrez, S. et al. 2008, "A new hazard index of complex mixtures integrates bioconcentration and toxicity to refine the environmental risk assessment of effluents", Environment International, vol. 34, no. 6, pp. 773-781

2. Point of Departure Index (PODI)

The Point of Departure Index (PODI) is derived in a similar fashion as are the Hazard Indices. The main difference is however that in order to derive PODI the concentration of the substance in the mixture is not compared to its acceptable safe threshold level (like e.g. the DNEL) but directly compared to the respective points of departure such as the no-observed-adverse-effect level (NOAEL), benchmark dose (BMD) or lower limit on the BMD (BMDL) values derived from the animal data. Again you might recognize the similarity to the Margin of Exposure (MoE) approach for single substances – in both cases the assessment / uncertainly factors that are already taken into account with the derived threshold levels are missing from the equation.

$$PODI = \frac{\text{Exposure level}}{\text{Point of departure value from animal data or NOAEL}}$$

For the evaluation of potential risk the PODI of a mixture is compared to an agreed "mixture" safety factor. This factor is often 100 (but an alternative value can apply) and the product of PODI and the uncertainty factor should be <1 to ensure safety.

For more information please refer to:

- Health and Environment Integrated Methodology and Toolbox for Scenario Development (HEIMTSA): Methodologies for quantifying health effects of exposure by multiple routes and the effects of mixtures in the light of the case studies. http://www.heimtsa.eu/LinkClick.aspx?fileticket=4L9vjvAiYO0%3D&tabid=2937&mid=6403

- Report of a WHO/IPCS Workshop on Risk Assessment of multiple chemicals http://www.who.int/ipcs/methods/harmonization/areas/workshopreportdocument7.pdf

ADDENDUM 1
Assessing Toxicity of Mixtures

3. Relative Potency Factors (RPF)

The method weighs the toxicity of the less toxic component as fractions of the toxicity of the most toxic ingredient (the substances that causes an adverse effect at the lowest concentration level). Each chemical is attributed a specific factor (RPF). This factor indicates the degree of toxicity compared to the most toxic ingredient, which is given a reference value of 1.To calculate the total toxic equivalent of a mixture, the amounts of each toxic compound are multiplied with their RPFs and then added together. Be aware that RPF values can vary for test data from different animal species. For example: Dioxin-based mixtures (assumes actions of the components of the mixture via the same mode of action) so called Toxicity Equivalency Factors (TEF) are calculated.

For more information please refer to:

- US EPA report on Developing Relative Potency Factors for Pesticide Mixtures (oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=427398)

4. Combined margin of exposure (MoE) for a mixture

The margin of exposure (MoE) of a substance (see page 118) is the NOAEL divided by exposure so that the combined margin of exposure of a mixture (MoEmix) can be calculated as

$$\text{MoE (single substance)} = \frac{\text{NOAEL or POD value}}{\text{Exposure}}$$

$$\text{MoE (mixture)} = \frac{1}{(1/MOE_1) + (1/MOE_2) + (1/MOE_3)} \text{ etc.}$$

When the combined MoE of the mixture is greater than the chosen assessment / uncertainty factor (usually 100, but an alternative value can apply) the combined risk of the mixture is also is considered to be acceptable.

For more information please refer to:

- EFSA Opinion on existing methodologies to assess cumulative and synergistic risks from pesticides to human health (http://www.efsa.europa.eu/it/scdocs/doc/705.pdf) or
- Trends in Food Science (http://www.efsa.europa.eu/en/corporate/doc/publ081216trends.pdf)

5. Physiologically Based Pharmacokinetic (PBPK) models

Physiologically based pharmacokinetic (PBPK) modeling is a complex mathematical approach for predicting absorption, distribution, metabolism and excretion of chemicals. These models can also be utilized for assessment of mixtures. By linking the individual chemical components in a chemical mixture at the level of pharmacokinetic and/or pharmacodynamic modeling, it is also possible to assess effects, collectively, of the chemical mixture of interest. This approach would only be performed when the above approaches could not exclude the mixture as being a concern.

For more information please refer to:

• US EPA: Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment (External Review Draft 2005) http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=135427

• WHO / IPCS Characterization and application of physiologically based pharmacokinetic models in risk assessment (http://www.who.int/ipcs/methods/harmonization/areas/pbpk_models.pdf)

6. Threshold of Toxicological Concern (TTC)

The Threshold of Toxicological Concern (TTC) approach has emerged over recent years from human health risk assessment approaches and is used to establish a human exposure threshold value for groups of chemicals below which there is no significant risk to human health. The TTC can be used to provide conservative estimates of the point of departure for chemicals substances that lack extensive toxicity testing. The value of this approach is limited since the estimates of toxicity are extremely conservative; however, it can be useful for the evaluation of trace contaminants in products (Price et al. 2009).

For more information please refer to:

• Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) Opinion on the Use of the Threshold of Toxicological Concern (TTC) Approach for the Safety Assessment of Chemical Substances (http://ec.europa.eu/health/ph_risk/committees/documents/sc_o_001.pdf)

• Price P, Wiltshire G. Modeling the chronic non-cancer effects of mixtures of migrants using Cramer classes and quantitative models of uncertainty. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2009 Dec;26(12):1547-55.

ADDENDUM 1
Assessing Toxicity of Mixtures

7.   Critical component approach

The critical component approach as outlined in the ECHA Guidance for downstream users (ECHA 2008) relies on DNEL and PNEC for all substances, their concentrations in the mixture and substance- and use-specific availability parameters indicating their potential for exposure. The critical component approach has its limitations because it requires availability of DNEL and PNEC for all substances in the mixture and knowledge on the detailed composition of mixtures obtained from other suppliers (for all substances with DNEL, irrespective of whether they are above or below the concentration limits for a classification of the mixture), which often would be considered confidential information.

Therefore, other ways were sought to identify lead substances in a mixture. An alternative method, which was developed by industry, is the DPD+ method.

For more information please refer to:

*   CEFIC REACH Practical Guide on Exposure Assessment and Communication in the Supply Chains Part III: Mixtures under REACH (http://www.cefic.org/Documents/IndustrySupport/REACH_Practical_Guide_Part_III_Mixtures_FINAL_CEFIC.pdf)

8.   Dangerous Preparation Directive (DPD+) Methodology

The Dangerous Preparations Directive (DPD, Directive 1999/45/EC) requires a mixture to be classified, if endpoint-specific concentration limits are exceeded by an individual component of the mixture, which itself is already classified based on its toxicological and/or ecotoxicological properties. Defined concentrations limits are used as an indicator of the hazard associated with the substance and are compared to the concentration of the substance in the mixture.

In Annex I of the methodological description of DPD+, generic concentration limits from DPD for all R phrases are listed and assigned to exposure pathways (http://www.cefic.org/Documents/IndustrySupport/REACH_Practical_Guide_Part_III_Mixtures_FINAL_CEFIC.pdf). The ratio calculated from the sub-stance concentration of a substance in a given mixture and its defined concentration limit (based on the single substance classification) is called Lead Substance Indicator (LSI).

$$LSI = \frac{\text{Concentration of a substance in a given mixture}}{\text{Defined concentration limit}}$$

LSI is to be calculated separately for inhalation, dermal, oral and eye exposure and for the aquatic environment. The substance with the highest LSI per pathway is selected as lead substance. In the methodological description, it is emphasized that when LSIs of two substances differ by less than 10%, both substances should be considered lead substances. Moreover, when two or more substances with the same health endpoint are contained in a mixture, which may lead to additive effects, the total amount of these substances should be taken into consideration, when identifying adequate risk management measures.

Note: Expert judgment is needed in this case to decide whether the sum of the risk characterization ratios has to be used in the assessment. Consideration of environmental effects is not as differentiated as toxicological effects as only few risk phrases for the environment exist in the current classification system. In addition, as the DPD does not contain concentration limits for R phrases R54 to R57 (toxic to fauna, flora, soil organisms, or bees), the scope of DPD+ is limited to effects on the aquatic environment.

The following minimum information is required for application of DPD+:

> Identity and concentration of hazardous substances in a mixture
> Classification of substances (R phrases)
> Specific concentration limits for substances, if available
> Vapor pressure of substances

For more information please refer to:

• CEFIC Guidance on "Methodology for the identification of substances that represent the dominant risks to human health and/or the environment and the drivers for risk management measures" (http://www.cefic.org/Documents/IndustrySupport/ES_for-preparations-DPD+methodology.pdf).

ADDENDUM 1
Assessing Toxicity of Mixtures

Amount of data needed to apply the method	Method	When used
Basic 1st Tier	• Threshold of Toxicological Concern (TTC)	
Basic 1st Tier	• Hazard Index (HI) • Cumulative Risk Index (CRI)	• 1st Tier Approach based on assumption of same mode of action • For workplace, environment and consumer
Basic 1st Tier	• Combined margin of exposure (MOE)	• For workplace, environment and consumer
Advanced 2nd Tier	• Dangerous Preparation Directive (DPD) + Methodology	• Available Classification and Labeling information (only applicable hazardous substances) would be the minimum requirement for this approach • Still under development and the main focus was workers exposure
Advanced 2nd Tier	• Point of Departure Index (PODI)	• For workplace, environment and consumer
Data rich 3rd Tier	• Physiologically Based Pharmacokinetic (PBPK) models	
Data rich 3rd Tier	• Relative Potency Factors (RPF) • Toxic Equivalent Factors (TEF)	• When data for a given chemical class is readily available (e.g., dioxins) • For workplace, environment and consumer
Data rich 3rd Tier	• Critical component approach	• Only applicable if you have sufficient hazard endpoint data (data rich substances) • Still under development and the main focus is worker exposure

Advantage	Disadvantage	Remarks
• The threshold value can be identified for many chemicals including those of unknown toxicity when considering their chemical structures	• Not applicable for bioaccumulative, allergenic, or endocrine disrupting substance	• Not specific methods for mixture assessment, but for chemical risk assessment as such
• Simple to use • Conservative	• Not applicable for non-genotoxic /non-threshold carcinogenic mode of action. This index is affected by assessment factors • Assumes that all components have the same mode of action	• Can be used when information is available. • Can be justified to focus only on components of the mixture that are key to the overall toxicity
• Relate directly to exposure and toxicity data	• No criteria for defining the magnitude of an acceptable MOE	
• Evaluable by SDS information, such as composition and hazard classification for substances in mixture	• Substances classified as CAT 1 or 2 carcinogenic, mutagenic or reprotoxic, as respiratory sensitizers or identified PBT-, or vPvB-substances are beyond the scope of the DPD+-method. Preparations containing safety-relevant concentrations of such substances will require an advanced evaluation. DPD does not contain concentration limits for R phrases R54 to R57	
• Relate directly to exposure and toxicity data	• No criteria for defining the magnitude of an acceptable PODI	
• Decrease the uncertainty for animal to human extrapolation	• Require biological parameter and physiological parameter	
• Relate directly to exposure and toxicity data • Simple to use. If justified for a specific class of chemistry, generally, widely acceptable	• Rely very much on the toxicity data for the index compound • Requires data for a relatively large proportion of chemicals of a given class	
• Discussed in REACH guidance for Downstream users	• Require composition, DNEL and PNEC for substances in mixture	

ADDENDUM 2

Workplace Risk Assessment

Purpose

GPS promotes the safe use of chemical products and enhances product stewardship throughout the value chain. This addendum was primarily written as an extension to the GPS strategy by providing a methodology for Companies to comprehensively assess potential exposures to chemical substances for those workers located at their manufacturing or other third party sites (e.g., potential exposures when handling process materials & feedstocks, additives, maintenance chemicals, insulations, coatings, wastes, etc).

This addendum can also be used to supplement the GPS "workplace exposure" assessment methodology by providing further guidance to assist in the evaluation of potential worker exposures for customers who purchase and handle products throughout the value chain (i.e., where "use" data may not be readily available or sufficient, this chapter provides guidance on the types of information to gather and a step-by-step approach to conduct a thorough worker risk assessment to evaluate those potential exposures). In addition, it can assist in determining if recommended risk management measures are adequate to ensure safe handling of products by downstream users. For example, this methodology can be used to assess if existing or recommended controls are adequate for the intended handling of the product by downstream users or if additional controls or recommendations are needed at their workplace.

Introduction

Occupational Hygiene (OH) is defined as the science and art of anticipating, recognizing, evaluating and controlling health hazards in the workplace. An additional element of verifying the effectiveness of established engineering controls through quantitative exposure monitoring of the affected workers improves the success rate of protecting workers' health. The need for an effective on-site OH program is essential to protect the health of the workers who may come into contact with chemical substances during the course of their employment.

An OH risk assessment program represents a comprehensive, systematic, and organized approach to assessing, analyzing, and managing occupational health risks in the work place. It should be designed as an on-going and iterative process that reflects changing operatin g conditions and potential health risks. It combines worker exposure information with the hazards associated with the chemical substances on a Risk Matrix that identifies the relative risk associated with that exposure. The frequency (or likelihood) in the risk matrix can be represented by the level/intensity of potential worker exposure and the consequence by the hazard classification of the substance.

This chapter focuses on how to establish a comprehensive OH risk assessment program to help ensure worker safety when handling / coming into contact with chemicals in their work environment.

Figure 6: OH Risk Assessment Overview

Inputs	Process	Outputs
BUSINESS • Operations Data • Chemical Substances • Worker Interviews • Work tasks / activities **FUNCTIONAL** • Health Regulation • Hazard Information • Air Monitoring Results • Previous Assessment Results	Basic Charaterization / Exposure Analysis / Risk Assessment Worker Groups / Initial Assessment / Risks Analysis Tasks / Exposure Rating / Controls Recommendations Work Areas / Monitoring Data / Results Communication Agents	**BUSINESS** • Health Risk Assessment and Management • Health Risk Communication • Engineering Controls PPE **FUNCTIONAL** • Common Global System • Focused Air Monitoring and Medical Surveillance • Data Validity and Inter Site Comparison • Preferred Practice Sharing

Objective

The objective of an OH risk assessment program is to enhance and standardize workplace exposure/health risk assessment and management. The results should be used by operating sites/locations to:

• Identify health risks requiring further assessment/control
• Communicate health risks to management and employees
• Respond to exposure related questions/concerns
• Identify opportunities for preferred practice sharing across work sites
• Prioritize air monitoring needs to determine worker inhalation exposures
• Focus medical surveillance
• Demonstrate regulatory compliance
• Document the adequacy of existing controls

ADDENDUM 2
Workplace Risk Assessment

Scope

This chapter covers occupational health risk assessments associated with chemical substances in the work place. Other environmental stressors such as physical agents (e.g., noise, radiation, heat & cold stress) and biological agents are not within scope of this chapter but should be considered in all comprehensive OH risk assessment programs. In addition, this chapter will focus on the assessment of potential inhalation exposures. Where potential dermal exposures are encountered; the recommended course of action is to either eliminate the potential exposure or to control it with the use of proper personal protective equipment (e.g., chemical protective gloves, chemical suits, etc). In addition, if dermal exposures occur, workers should be instructed to immediately wash the affected area with soap and water and to always decontaminate before eating, drinking or any other activity that could lead to potential ingestion (i.e., to minimize potential oral exposures).

Section One: Basic Characterization
Step 1: Establishing the Exposure Assessment Strategy

Establishing an OH risk assessment strategy begins with identifying the risk assessor, establishment of assessment goals and the development of a written program.

1. **The Risk Assessor** - the individual that conducts the risk assessment should have basic training in occupational health or industrial hygiene or work under the direction of an OH professional since professional judgment will be relied upon during the course of the assessment.

2. **Exposure Assessment Goals** - goals should be established before embarking upon the assessment process. A comprehensive OH risk assessment program should focus on assessing and controlling all potentially hazardous substances on site. A subset of the program could be compliance driven (i.e., focus on demonstrating compliance with established regulatory or voluntary occupational exposure limits (OEL)).

3. **Written Exposure Assessment Program** - a written program should be established for documenting how an organization will implement the OH risk assessment program at their site. It should specify the strategies, methods and criteria used in performing the assessments.

Step 2: Gather Information

The initial phase involves the collection of basic information that will facilitate the selection of substances and work activities (i.e., exposure scenario) for which to conduct a full exposure assessment. Note: the initial phase should be approached as a "screening phase"; where the assessor should gather information with the understanding that it is typically not necessary to fully assess every exposure scenario. Focus should be to identify and prioritize those exposure scenarios where there is a potential to exceed an occupational exposure limit that may require additional controls or risk management measures to minimize worker exposures or where the potential expoures are unknown (i.e., need more data). Where a potential exposure scenario is already well controlled with no or relatively low exposure potential to the workers and there is no evidence of worker illness in the workplace, then there is no need to do a full occupational exposure assessment and the initial determination should be documented as complete. This step includes the collection of the following information:

1. **Process Information** - process descriptions and flow diagrams are helpful to identify where potential exposures to chemical substances may occur (e.g., open versus closed systems, continuous or batch operations, etc.). They also provide an overview of the process chemistry and additives which will help in the identification of potentially hazardous substances on site. In addition, identify existing controls in place (or lack thereof) that are designed to minimize worker exposures to these substances (e.g., exhaust ventilation, manual versus automated systems, etc).

2. **Maintenance Information** - maintenance activities typically have a higher potential for exposure since they can involve direct contact with the process (e.g., repair of pumps, cleaning vessels, ov erhaul equipment). A review of the typical maintenance activities and procedures will help identify where there is a potential for direct exposure to the process chemicals.

3. **Workforce** - organization charts, job descriptions, a list of tasks or activities that workers perform are very helpful to identify where workers c ould encounter potentially hazardous substances. Worker interviews are important to identify specific tasks or activities where they may encounter exposures to chemical substances during the course of their job. Consider both routine and non-routine activities when collecting this information; as it is the non-routine activities where some of the more hazardous exposures can occur.

4. **Chemical Substances** - an inventory of purchased and process chemicals should be identified and maintained on site (e.g., site Hazard communication program). When reviewing the inventory look for potentially hazardous substances that the workers may come into contact, based on the workforce data collected above.

Another potential for exposure can occur with "isolated intermediates" which are substances never packaged, but may be found in pumps, reactors and pipes.

ADDENDUM 2
Workplace Risk Assessment

5. **Hazard Information and OELs** - gather available hazard information for the substances on site (i.e., reference "Step 2" in the Guidance on Chemical Risk Assessment Strategy). In addition, gather OELs for the substances of concern. Many governments have established OELs for their jurisdiction and where none exist, non-governmental organizations like the American Conference of Governmental Industrial Hygienists publish Threshold Limit Values (TLVs) that can be used (http://www.acgih.org/home.htm). The American Industrial Hygiene Association also establishes peer-reviewed Workplace Environmental Exposure Limits (WEELs) for some less common, yet hazardous, chemicals in the workplace (http://www.aiha.org/Pages/default.aspx). Many companies have internal processes in place where they establish their own OEL's and publish them on their Safety Data Sheets. EU REACH DNELS at the following site are also helpful http://apps.echa.europa.eu/registered/registered-sub.aspx#search. Finally, in the total absence of any published OEL's the assessor can establish a "working OEL" by reviewing available epidemiological and/or toxicological information or from drawing an analogy with a similar substance that already has an OEL. A working OEL should have a large safety factor to account for the lack of data.

6. **Exposure Monitoring Data** - gather existing air monitoring or other data that has been collected to assess potential worker exposures on site. This data can consist of full shift or task data that has been collected by standard Industrial Hygiene monitoring methods or by direct read instruments used to quantify potential exposures at the time of a task or activity. If no data exists on site, exposure information can be obtained from various peer reviewed publications or from Government or University Websites:
    - OH journals (e.g., Journal for Occupational and Environmental Hygiene at http://www.aiha.org/news-pubs/Pages/JOEH.aspx or
    - Annals of Occupational Hygiene at http://annhyg.oxfordjournals.org/
    - Government agencies (e.g., United States National Institute for Occupational Safety and Health at http://www.cdc.gov/niosh) or Universities with Occupational Health and Safety degree programs.

Step 3: Conduct a Basic Characterization

Exposure assessments should be performed on groups of workers who conduct the same or similar work activities in the same Work Areas, and thereby have similar exposure potential to those hazardous substances located in those work areas (i.e., Similar Exposure Groups - SEGs). During this phase the assessor should begin to compile a list of tasks and activities for each SEG which they may want to conduct a risk assessment.

During this phase is when the assessor should rely on past exposure monitoring data and professional judgment to screen out those tasks and activities where there is very limited potential to exceed an OEL (i.e., < 10% of OEL).

Organization Charts and SEGs

Organization charts typically identify "positions" that are staffed by workers on a daily basis. In most cases these positions will be the SEGs as they perform a pre-defined set of tasks and activities in a defined work area within the site and have exposure to similar substances during their daily activities.

Where "positions" work in multiple crafts or across different Work Areas, it may be necessary to sub-divide these positions into separate SEGs according to the unique combination of Work Area and Craft they perform and is primarily based on the combination of similar exposure tasks they perform. For example, a job title for a group of workers might be "Maintenance Technician". In this case it would be appropriate to split this into several SEGs depending upon the crafts that are performed as their exposure profile might differ (e.g., Welders, Instrument Technicians, Electrical Technicians, custodians, etc).

Work Areas

The overall operating site can normally be divided into one or several Work Areas that consist of geographic boundaries where groups of workers are normally assigned on a day to day basis (i.e., based on their job description). The most efficient Work Area definition will typically be consistent with the existing operation's definition of the areas (e.g., operating units, zones, process areas, etc). One exception may be Maintenance workers as they may service all work areas within an operating site.

Tasks / Activities

Not all tasks that a SEG perform will need to go through a formal risk assessment.
Efforts should focus on those tasks or work activities performed by a SEG that may result in exposures above or near an OEL (i.e., potentially > 50%). In addition, consider assessing Tasks that meet the following criteria:
• Involve a chemical substance with a regulatory emphasis or is a substance of concern
• Complaints from work ers (e.g., irritant, smell, etc)
• New operations or activities where no other exposure data is available

Chemical Substances

During this phase the assessor should identify those "Substances" to which a worker may be exposed which could have adverse health effects. They can include chemicals that may be present as raw materials, process intermediates, products; or that may arise in the course of operations.

ADDENDUM 2
Workplace Risk Assessment

Section Two: Risk Assessment
Step 4: Exposure Analysis

Based upon the information gathered during the basic characterization phase, a list of SEGs, tasks and chemical substances (i.e., exposure scenarios) for which the assessor wishes to conduct an exposure analysis should be compiled. The exposure analysis involves assigning an exposure intensity to a chemical substance for that given task or activity as compared to the identified OEL. This phase involves the following two steps:

Identify Exposure Scenarios - Identify SEG exposure Scenarios (i.e., selected tasks and associated substances that may result in significant exposure for the task or activity).

Exposure Ratings - Assign exposure intensity ratings to each exposure scenario (i.e., tasks and applicable substance combinations). The exposure ratings should be based on potential airborne exposures as compared to relevant OELs. Ideally, exposure ratings will be based on historical air monitoring data which quantitatively measures the airborne exposure levels in the workers breathing zone. When limited or no previous data exists, exposure ratings can be estimated by using one of the following techniques (refer to the reference documents at the end of this chapter for supplemental information on how to estimate exposures when limited data exist or when there is no OEL for a substance):
* Obtain "screening level" measurements of the exposure scenario using direct reading instruments (e.g., detector tubes, gas detecting devices, etc).
* Surrogate estimates can be based on similar substances handled in a similar manner where data or knowledge is available.
* Exposure modeling tools are available to estimate potential exposures.

The exposure rating applied to each task / substance combination should reflect the typical exposure category when performing this activity. The exposure rating should be assigned without regard for personal protection (e.g., respiratory protection) as it should reflect the estimated airborne concentration (i.e., personal protective equipment is considered the last line of defense from a hierarchy of controls perspective); however, when OELs are exceeded protective measures, such as personal protective equipment, must be in place to help minimize those exposures until more robust engineering controls can be put in place.

The following is an example of how exposure ratings might be assigned:

Exposure rating:

A   At or Above OEL

B   ≥ 50 - < 100% OEL

C   ≥ 10 - < 50% OEL

D   NIL - < 10% OEL

Step 5: Hazard Classification

The Hazard Classification should be consistent with the UN GHS hazard endpoints for that substance and the Priority system described in Section One Step 3 in this Guidance Document. Select the highest human health hazard level for each substance using the Table 3: Assessing the intrinsic hazard of chemicals for the GPS Priority allocation system; a) Human health (based on GHS classification criteria).

Step 6: Risk Assessment

A health risk assessment is conducted by plotting the exposure rating for the task and substance of concern with the hazard classification for the substance on a Risk Matrix. The exposure rating is placed on the probability axis, the Hazard Classification on the consequence axis. Risks are assessed on a priority basis to determine follow-up actions. As demonstrated below, the goal is to reduce the risk by reducing the exposures.

ADDENDUM 2
Workplace Risk Assessment

Exposure rating

	A	B	C	D
1				
2	X	Risk Mitigation →		Y
3				
4				

Hazard classification
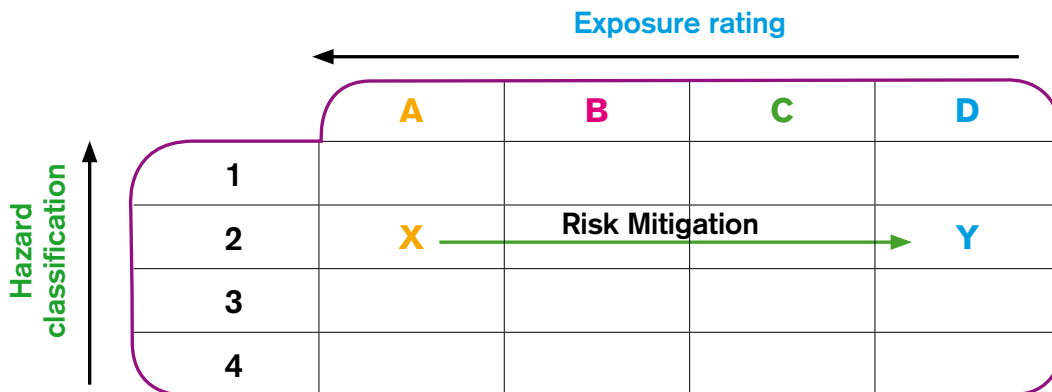
An alternative but similar approach to the above is "Control Banding" from the UK Government, Health and Safety Executive (see reference at the end of this Chapter). Control banding assigns a hazard class based on EU Risk phrases (R phrases). Exposure bands are then assigned to a Control Band based upon three exposure determinants: quantity, physical form and existing control. The outcome is one of four recommended control strategies:
(1) use good industrial hygiene practice,
(2) use local exhaust ventilation,
(3) enclose the process or
(4) seek the advice of an expert.

Section Three: Risk Management & Communications
Step 7: Risk Management Category (RMC)

The RMC (reference Figure below) provides a prioritization of the potential Occupational Health risks associated with the workplace exposures. The RMC is used to determine if existing controls are appropriate or need enhancement. It is also used as a communication tool and to plan additional follow-up activities (e.g., air monitoring, surveillance, testing of engineering controls, ensuring site procedures include steps to minimize exposures, etc). Examples of actions associated with the Action Categories include:

Category 1 is generally associated with confirming the effectiveness of existing exposure controls and developing plans to reduce further the potential for exposure. This may include engineering, administrative, and personal protective equipment controls. This action category generally also results in more detailed exposure analysis, including task specific exposure assessment and monitoring, worker training, and may include medical monitoring and surveillance. The goal is to reduce exposures in this category.

NOTE: Category 1 exposure should be controlled with personal protective equipment until the exposure rating category can be reduced to an acceptable level with engineering or administrative controls as described in "Step 8 - Risk Control" below.

Category 2 is generally associated with ongoing surveillance and monitoring, and continuous improvement in procedures and equipment to reduce further the potential for exposure. This may include more detailed exposure analysis, including task specific exposure assessment and monitoring, worker training, and medical monitoring and surveillance.

Category 3 generally results in periodic reassessment to determine if conditions have changed, and additional worker hazard awareness communication is needed.

Exposure rating category

←

	A	B	C	D
1	1	1	2	2
2	1	1	2	3
3	1	2	3	3
4	2	3	3	3

Hazard classification ↑

Red = confirm controls
Yellow = continuous improvement & ongoing monitoring
Green = periodic reassessments

ADDENDUM 2
Workplace Risk Assessment

Step 8: Risk Control

The following hierarchy of control is recommended to control potential occupational health hazards in excess of established OEL's:

- Elimination or substitution of the process, equipment or materials giving rise to the exposure
- Engineering controls (e.g., enclosures, local exhaust ventilation, etc)
- Work practice controls (e.g., using wet methods to suppress dust) and employee training
- Administrative controls (e.g., restrictions or redeployment of workers to minimize exposures)
- Proper selection, fitting and use of personal protective equipment

References:

- American Industrial Hygiene Association, (AIHA): A strategy for Assessing and Managing Occupational Exposures, Third Edition. Ignacio, j. and W. Bullock (eds.). Fairfax, VA: AIHA, 2006.

- American Industrial Hygiene Association, (AIHA): Mathmatical Models for Estimating Occupational Exposure to Chemicals. Charles Keil (ed.). Fairfax, VA: AIHA, 2000.

- UK Government, Health and Safety Executive, "Control of Substances Hazardous to Health", http://www.hse.gov.uk/coshh/

- American Industrial Hygiene Association, (AIHA): Guidance for Conducting Control Banding Analysis. Fairfax, VA: AIHA, 2007.

GLOSSARY
DEFINITION OF TERMS USED IN THIS DOCUMENT

Term	Definition
Additives	A second substance that has been intentionally added to stabilise the first substance which contributes to the substance composition (but not to the naming).
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	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 guidance[48] document see www.inchem.org/documents/harmproj/harmproj/harmproj2.pdf 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).
Benchmark Dose or Concentration	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. 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).
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	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. www.rivm.nl/en/healthanddisease/productsafety/ConsExpo.jsp
DEREK	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. www.lhasalimited.org
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).
DMEL (Derived minimal effect level)	Expresses an exposure level corresponding to a low risk. Excess lifetime risk: how many excess cases in absolute terms will result from a given relative estimate of risk. Cancer risk levels of 10-5 and 10-6 could be seen as indicative tolerable risk levels when setting DMELs for workers and the general population, respectively.
DNEL (Derived no effect level)	The level of exposure above which humans should not be exposed. DNELs are for threshold effects.
EASE (Estimation and Assessment of Chemical Exposure)	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. 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.

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/episuitedl.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://ihcp.jrc.ec.europa.eu/our_activities/health-env/risk_assessment_of_Biocides/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 substance, as produced that does not contribute to the naming of the substance. Identification and quantification of impurities is required for all impurities (including isomers and by-products) if above 1 % and those impurities from 0.1 % onwards that are relevant for the hazard classification and/or PBT assessment.

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	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	Mixture in the context of the GPS risk assessment refers to a preparation (or formulation) intentionally produced with known composition and sold into commerce that is composed of two or more chemical substances (and their impurities) and will result in simultaneous exposures of the substances to an individual.
Mono-constituent substance	Concentration of the main constituent 80% (w/w).
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
Multi-constituent substance	More than one constituent 10% and < 80% (w/w).
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	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	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. http://oasis-lmc.org/?section=software&swid=4
OECD	Organization for Economic Co-operation and Development. www.oecd.org
OECD Test Guidelines	The OECD Test 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. http://www.oecd.org/env/testguidelines
OECD SIDS program	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. http://www.oecd.org/env/existingchemicals http://www.oecd.org/env/existingchemicals/data
OECD QSAR 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 categories. http://www.oecd.org/env/existingchemicals/qsar
Point of Departure (Starting point)	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. www.epa.gov/NCEA/iris/help_gloss.htm#p

GLOSSARY
DEFINITION OF TERMS USED IN THIS DOCUMENT

Term	Definition
Preparation, also called mixture	Mixture in the context of the GPS risk assessment refers to a preparation (or formulation) intentionally produced with known composition and sold into commerce that is composed of two or more chemical substances (and their impurities) and will result in simultaneous exposures of the substances to an individual.
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
Substance	Means a chemical element and its compounds in the natural state or obtained by any manufacturing process, *including* any additive necessary to preserve the stability and impurity deriving from the process used, but *excluding* any solvent which may be separated without affecting the stability of the substance or changing its composition.
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. http://accelrys.com/mini/toxicology/predictive-functionality.html
Toxicology	Toxicology (from the Greek words Τοξικος - 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.
UVCB (Unknown or Variable composition Complex reaction product or Biological origin)	No differentiation between main constituents and impurities, identity of constituents should be given as far as known > 10% and identification of constituents relevant for classification and/or PBT assessment.

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.ec.europa.eu/home.php
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
OECD Environmental Risk Asessment Toolkit	http://www.oecd.org/env/riskassessment/toolkit
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

ANNEX 2
DETAILED LIST OF CONTENTS

ANNEX 2
DETAILED LIST OF CONTENTS

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
    http://live.unece.org/trans/danger/publi/ghs/ghs_rev02/02files_e.html
10 http://www.oecd.org/env/testguidelines
11 www.iso.org/iso/home.htm
12 http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html
13 www.astm.org
14 http://echa.europa.eu/legislation/reach_legislation_en.asp
15 www.epa.gov/oppt
16 www.meti.go.jp/english/information/data/TESTindex.html
17 For additional guidance on grouping of chemicals see http://www.oecd.org/document/6/0 ,3343,en_2649_34379_43087494_1_1_1_1,00.html
19 http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_ r6_en.pdf?vers=20_08_08
20 http://guidance.echa.europa.eu/docs/guidance_document/information_require- ments_r4_en.pdf?vers=20_08_08 and http://www.oecd.org/document/23/0,3343, en_2649_34379_33957015_1_1_1_1,00.html
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 For details, refer to chapter R.10 in the Guidance on Information Requirements and Chemical Safety Assessment of REACH.
24 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
25 www.epa.gov/nrmrl/std/cppb/qsar/index.html#TEST

[26] www.multicase.com/
[27] www.lhasalimited.org/
[28] http://accelrys.com/mini/toxicology/predictive-functionality.html
[29] www.compudrug.com
[30] www.multicase.com
[31] http://iccvam.niehs.nih.gov/methods/acutetox/inv_nru_brd.htm
[32] www.oecd.org/dataoecd/39/12/34446120.pdf
[33] www.ncbi.nlm.nih.gov/pubmed/16522150
[34] www.springerprotocols.com/Abstract/doi/10.1385/1-59745-037-5:371
[35] www.ncbi.nlm.nih.gov/pubmed/15588167
[36] www.ncbi.nlm.nih.gov/pubmed/15588168
[37] www.oecd.org/document/54/0,3343,en_2649_34379_42923638_1_1_1_1,00.html
[38] http://chm.pops.int/
[39] www.pbtprofiler.net/
[40] US NRC, 1991a.
[41] http://ec.europa.eu/competition/mergers/cases/index/nace_all.html
[42] www.oecd.org/document/46/0,3343,en_2649_34373_2412462_1_1_1_1,00.html
[43] www.ecetoc.org/tra
[44] http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_part_d_en.pdf
[45] www.cefic.org/files/downloads/RMM%20Library%20.xls
[46] http://reach.bdi.info/378.htm
[47] http://reporting.responsiblecare-us.com/Search/PSSummarySearch.aspx
[48] www.ecetoc.org/tra

ICCA
Avenue E Van Nieuwenhuyse 4, box 1
B-1160 Brussels, Belgium

www.icca-chem.org

Responsible Care®
OUR COMMITMENT TO SUSTAINABILITY