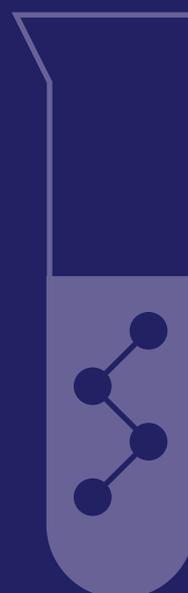
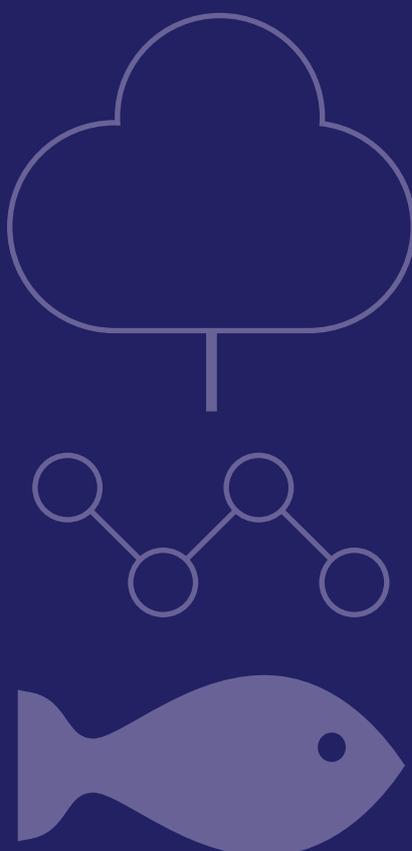
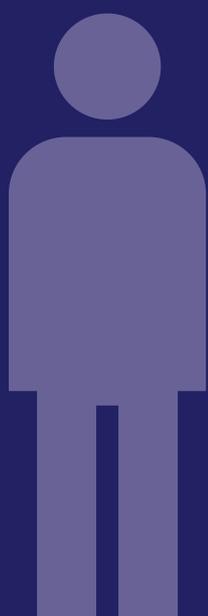


Guidance on national chemicals control

Hazard and risk assessment of chemicals – an introduction

GUIDANCE 7



The Swedish Chemicals Agency's guidance series on national chemicals control

This guidance is part of a series developed by the Swedish Chemicals Agency. The guidance documents cover a wide range of issues that are important for the establishment of a system for preventive chemicals control. First versions of the documents were published during 2017 to 2020.



Control of chemicals placed on the market (brochure)



1. Sustainable financing of institutional capacity for chemicals control



2. Risk reduction of chemicals



3. Legislation on chemicals placed on the market



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6. Hazard and risk assessment and risk reduction of pesticides



7. Hazard and risk assessment of chemicals – an introduction

Link to the guidance documents and more information on guidance on national chemicals control: www.kemi.se/en/guidance-on-national-chemicals-control



KEMI

Swedish Chemicals Agency

The Swedish Chemicals Agency is supervisory authority under the Swedish Government. We work in Sweden, the EU and internationally to develop legislation and other incentives to promote good health and improved environment. We monitor compliance of applicable rules on chemical products, pesticides and substances in articles and carry out inspections. We also provide guidance regarding enforcement and inspections to municipalities and county administrative boards. We review and authorise pesticides before they can be used. Our environmental quality objective is A Non-toxic Environment.

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Cover illustrations by Maja Modén

Document history

Version 1.0

First Edition

Guidance 7

November 2020

Preface

Chemicals contribute in many ways to improving our standard of living, but some of them are hazardous and can have serious adverse effects on human health and the environment. It is therefore necessary to use different means to protect human health and the environment from adverse effects emanating from exposure to hazardous chemicals.

This guidance is part of a series of guidance documents developed by the Swedish Chemicals Agency. The series forms a complement to the UNEP Guidance on the Development of Legal and Institutional Infrastructures and Measures for Recovering Costs of National Administration (LIRA guidance) by providing more detailed guidance in different areas. This guidance is intended as an introduction to hazard assessment and risk assessment of chemicals in order to provide a better understanding of the key concepts and overall methodology.

The Swedish Chemicals Agency has developed this guidance with the financial assistance of the Swedish International Development Cooperation Agency (Sida). The views herein shall not be taken to reflect the official opinion of Sida.

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Summary

This guidance is an introduction to hazard assessment and risk assessment of chemicals. It presents key terms and concepts and explains the general approach.

In the context of chemicals management, hazard means the ability of a chemical substance or mixture to cause harm and risk relates to the probability to cause harm under certain conditions. While hazard is an intrinsic property of the chemical, risk varies depending on exposure to the chemical.

The hazard of chemical substances is frequently assessed by using test systems and comparing the test results with preset criteria for specific effects.

The risk depends on the hazard in combination with exposure. Exposure can be measured or, more frequently, estimated by using exposure models. Such models cover e.g. how chemicals are used, emitted, and their fate in the environment as well as within the human body.

The guidance underscores the importance of defining responsibilities of different actors such as producers and importers of chemicals and authorities in legal text. It is important to adapt the assessment to the purpose of it. Previously available information should be used as much as possible. The guidance provides an insight into the EU system of hazard assessment and risk assessment and provides links to sources of further information on the process and data on chemicals.

Definitions and acronyms

Chemicals (or chemical products) are usually defined and understood as chemical **substances** and **mixtures** of chemical substances.

Substance means chemical elements and their compounds in their natural state or obtained by any production process, including any additive necessary to preserve the stability of the product and any impurities derived from the process used, but excluding any solvent, which may be separated without affecting the stability of the substance or changing its composition.

Mixture means a mixture or solution composed of two or more substances in which they do not react.

Many chemical products are incorporated in finished products, or **articles**. An article can be defined as an object that during production is given a special shape, surface or design which determines its function to a greater degree than does its chemical composition. Examples of articles are painted and lacquered furniture, polymers and metals in electric and electronic products, dyes in textiles, flame-retardants, and plasticizers in plastic products etc. Articles may pose a risk due to their chemical contents. In some countries, specific substances have been regulated in certain groups of articles, e.g. toys, but in general, articles are, to a large extent, unregulated with regards to their chemical contents.

Acronym	Explanation
ADI	Acceptable Daily Intake
AF	Assessment Factor
AOEL	Acceptable Operator Exposure Level
ARfD	Acute Reference Dose
BCF	Bioconcentration factor
BMD	Benchmark Dose
BMDL	Benchmark Dose Lower-confidence Limit
BPR	EU Regulation on Biocidal Products (No. 528/2012)
CLP	EU Regulation on Classification, Labelling and Packaging of Substances and Mixtures (No. 1272/2008)
CMR	Carcinogenic, mutagenic or toxic to reproduction
CSA	Chemical safety assessment
CSR	Chemical safety report
DMEL	Derived Minimal-Effect Level
DNEL	Derived No-Effect Level
EC ₁₀	Effect Concentration, ten percent of population/test organisms effected
EINECS	European Inventory of Existing Commercial Chemical Substances
ESD	Emission scenario document
ECETOC TRA	The Targeted Risk Assessment Tool of the European Centre for Ecotoxicology and Toxicology
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EU	European Union
EUSES	The European Union System for the Evaluation of Substances

FAO	Food and Agriculture Organization of the United Nations
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
HQ	Hazard Quotient
IARC	International Agency for Research on Cancer
IUCLID	International Uniform Chemical Information Database
IUPAC	International Union of Pure and Applied Chemistry
LOAEL	Lowest-Observed-Adverse-Effect-Level
LOEC	Lowest-Observed-Effect-Concentration
MRL	Maximum Residue Level
NOAEL	No-Observed-Adverse-Effect-Level
NOEC	No-Observed-Effect-Concentration
OECD	Organisation for Economic Co-operation and Development
PBT	Persistent, Bioaccumulative and Toxic
PEC	Predicted Environmental Concentration
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPPR	EU Regulation on Plant Protection Products (No. 1107/2009)
(Q)SAR	(Quantitative) Structure Activity Relationship
RCR	Risk Characterisation Ratio
REACH	EU Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals (No. 1907/2006)
RfC	Reference Concentration
RfD	Reference Dose
SDS	Safety Data Sheet
SF	Slope Factor
T _{1/2}	Half-life, e.g. the time it takes until the presence of a compound is halved, due to degradation
TER	Toxicity exposure ratio
UNEP	United Nations Environment Programme
UR	Unit Risk
US EPA	United States Environmental Protection Agency
WHO	World Health Organisation
vPvB	very Persistent and very Bioaccumulative

1 Introduction and scope

Chemicals form an important part of our daily life, but they may also pose risks to health and the environment depending on their intrinsic hazardous properties and how they are used. Hazardous chemicals can be present in products that are sold to professional users and to private consumers for use in everyday life. The use and subsequent dispersal of hazardous substances can jeopardise the long-term utilisation of land and water resources and make groundwater and fish, for example, unfit for human consumption. This in turn can have an adverse impact on the development of countries. People are exposed to chemicals at work, in their homes, and indirectly through the environment, which can lead to deaths or acute or long-term effects on health. Measures are taken to reduce such exposure in many countries, but there are wide differences today in the capacity of the world's countries to manage chemicals safely. The aim of the present document is to give guidance to countries (governments and authorities) in their efforts to set up an efficient system for the sound management of chemicals. In the Swedish Chemicals Agency Guidance "Risk reduction of chemicals" (Swedish Chemicals Agency, 2018)¹, practical advice is given on how to work with risk reduction of chemicals in a country. The purpose of hazard assessment and risk assessment is to serve as a technical background for risk reduction measures.

The sound management of chemicals requires national legislation that should define the tasks and obligations of different actors. It is important that legislation clarify the division of responsibilities between trade and industry on the one hand and national administration on the other hand. Therefore, when forming legislation, it should be considered how and by whom hazard and risk assessments should be done. It is advisable to at least place an obligation on producers and importers to assess the hazards of the chemicals they place on the market. This forms the basis for requirements on dissemination of information in the supply chain, which is a prerequisite for safe handling of chemicals¹. Chemicals legislation could also require producers and importers to perform risk assessments for the substances they produce or import. If the risk assessment shows that there is a risk at some stage of the substance's life cycle, companies could be required to supply relevant safety information to downstream users based on the assessment that has been carried out and to apply necessary risk-management measures to control the risk. Legal requirements need to be clear and there may be a need to also develop guidance material².

Despite any general obligations on trade and industry to handle risks, the government should always have the opportunity to perform assessments and be able to introduce bans, restrictions, and other risk-reducing measures. The government should, to be resource efficient, focus its regulatory work on substances posing the greatest risks. These substances might be identified through actual cases of pollution and poisoning, but it is advisable to try to identify potentially problematic substances before any harm has occurred. A systematic approach would build on the prioritisation of substances that, due to their known or assumed hazards and/or use patterns, are likely to give rise to risks that need to be eliminated, or at least reduced to an acceptable level.

Having legal structures in place where intrinsic properties giving rise to very severe or irreversible effects is enough for decisions on bans and restrictions, and enables countries to

¹ Swedish Chemicals Agency (2018). Guidance on national chemicals control: Risk reduction of chemicals. Retrieved 2020-09-21 from <https://www.kemi.se/en/international-cooperation/guidance-for-other-countries>

² Swedish Chemicals Agency (2018). Guidance on national chemicals control: Legislation on chemicals placed on the market. Retrieved 2020-09-21 from <https://www.kemi.se/en/international-cooperation/guidance-for-other-countries>

base a decision for risk reduction on hazard assessments (hazard-based approach). For other chemicals, a risk assessment should normally be carried out when considering the need for banning or restricting the use of a chemical (risk-based approach). When performing a risk assessment, it is necessary to have information both on the hazard of the substance and the potential exposure to the substance in the country because risk is a function of hazard and exposure.

It can be stated in legislation that producers and importers of chemicals have an obligation to provide the necessary data, including assessments made by them, to enable authorities to carry out their duties.

The intrinsic properties of a substance are the same regardless of country or use situation and hence all other available hazard data and assessments from other countries, organisations, and science could also be used as a basis for a hazard assessment. The exposure of the environment and the population to a substance might, however, vary from country to country. In some cases, especially when it concerns hazardous chemicals entering a country as a constituent in a product that is also used in other countries, it might be relevant to make use of risk assessments that are internationally available as far as possible in order to save resources and time. On the other hand, if it is clear that the use pattern or the volume of the substance differs significantly from countries where risk assessments has already been made, it would be necessary to undertake a national risk assessment taking into account the exposure in the country. Anyway, unless the chemical undergoing risk assessment is uniquely produced in the country, risk assessments from other countries could be used as a source of information.

Risk assessment models are generic and mainly scientific, although to what extent a risk can be considered “acceptable” by society is a matter of policy nature. There are, however, internationally adopted approaches on how to define “acceptable” risks, e.g. by organisations such as the FAO, WHO and OECD. In this document, the definition of an acceptable risk follows the definitions in documents published by these organisations.

When a risk is identified, subsequent decisions on risk reduction measures are needed. This is further discussed in the Swedish Chemicals Agency Guidance on risk reduction of chemicals (see footnote 1).

This guidance is intended as an introduction to hazard and risk assessment of chemicals to provide a basic understanding of the topic, and to introduce general principles and the overall methodology. It will help those developing legislation to consider the role of hazard and risk assessments when forming legislation. On a more concrete level, it will help authorities interpret and evaluate existing data on chemicals and existing assessments, both from industry and from other countries and organisations. For those who need to do a full risk assessment, it gives guidance to sources of further information on how to perform a risk assessment. The guidance also provides an understanding of what data is required for risk assessment of chemicals.

The following chapters (2-6) contain a step by step explanation of the various elements of a risk assessment. Chapter 7 briefly explains how chemicals are assessed within the EU legal system and gives guidance to useful information that can be found on the website of the European Chemicals Agency.

2 General concepts and principles of risk assessment

This introduction to risk assessment is mainly based on available guidance documents and the websites of international organisations, e.g. the WHO Human health risk assessment toolkit: chemical hazards³ and OECD Environmental risk assessment toolkit⁴.

It is important to distinguish between hazard and risk in the assessment of chemicals. While *hazard* refers to the intrinsic properties of a chemical, *risk*, or the probability of an adverse outcome (harm), considers hazard in conjunction with *exposure* (Box A). Exposure to a chemical means how and in which concentration a human or an organism get in contact with the chemical.

Box A The relationship between hazard and risk is commonly expressed as

$$\text{Hazard} \times \text{Exposure} = \text{Risk}$$

The basic steps in risk assessment of chemicals are hazard assessment, exposure assessment, and risk characterisation (Box B). Hazard assessment can be subdivided into hazard identification and hazard characterisation (or dose-response assessment).

Box B The basic steps in risk assessment of chemicals

- Hazard assessment
 - Hazard identification
 - Hazard characterisation (Dose-response assessment)
- Exposure assessment
- Risk characterisation

A simple way to define risk is the *probability of an adverse outcome*. When dealing with the risk assessment of chemicals, the nature of the adverse outcome depends on the intrinsic property of the chemical and the susceptibility of the target organism, while the probability also depends on the degree of exposure to the chemical. The purpose of a risk assessment is to provide technical support for decision makers. As risk assessment deals with probabilities, they always include an element of uncertainty, but the uncertainty should not be taken as an excuse not to act when evidence points to a risk⁵. This principle, *the precautionary principle*, was initially defined at the World Summit on Sustainable Development in Rio 1992:

“Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.”

³ WHO (2010). Human Health Risk Assessment Toolkit: Chemical Hazards. Retrieved 2020-09-21 from https://www.who.int/ipcs/methods/harmonization/areas/ra_toolkit/en/

⁴ OECD (2016). Environmental risk assessment toolkit. Retrieved 2020-09-21 from <https://envriskassessmenttoolkit.oecd.org>

⁵ European Commission (2000). Commission adopts Communication on Precautionary Principle. Retrieved 2020-09-21 from http://europa.eu/rapid/press-release_IP-00-96_en.htm

3 Hazard assessment

The hazard of a chemical depends on its intrinsic properties, i.e. its capacity to interfere with normal biological processes in living organisms, or its capacity to burn, explode, corrode, etc. Chemicals can be classified according to the type and severity of the hazard using set criteria and a systematic assessment of available test results and the scientific literature.

Hazard assessment means to identify the type of adverse effects that a chemical substance or a mixture of chemical substances can cause in an organism, population or ecosystem. Hazard data can therefore be used universally in risk assessment and risk reduction. Thus, it is important to search for available data on hazards as an initial step in a risk assessment. The present guidance focuses on the effects on biological systems, it does not deal with physical hazards (such as flammability, explosivity, oxidising properties) and risks associated with such properties.

3.1 Hazard identification

Hazard identification is the process of determining whether exposure to a substance can cause a specific adverse effect on human health or organisms in the environment.

An adverse effect is described by the International Programme on Chemical Safety (IPCS)⁶ as:

“Change in morphology, physiology, growth, reproduction, development, or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increased susceptibility to the harmful effects of other environmental influences.”

Chemical substances and mixtures can be classified as hazardous considering what types of adverse effects they may produce.

3.1.1 Finding and evaluating information on intrinsic hazardous properties

The hazardous properties of chemicals are usually identified by testing and applying different internationally accepted methods. In some cases, epidemiological studies and accident reports can be used. For many substances, data on intrinsic hazardous properties, established through testing, may be already internationally available through public databases. If no data is available, new testing may be considered.

A compilation of databases can be found on the OECD's eChemPortal⁷. It provides direct links to collections of chemical hazard and risk information prepared for government chemical review programmes at national, regional and international levels. In addition, eChemPortal also provides exposure and use information on chemicals.

The European Chemicals Agency (ECHA) maintains one of the world's largest freely publicly available regulatory databases on chemical substances⁸. It includes information from industry as well as EU member states and regulators. The database provides valuable information that

⁶ WHO (2004). IPCS Risk assessment terminology. Retrieved 2020-09-21 from <https://www.who.int/ipcs/methods/harmonization/areas/terminology/en/>

⁷ OECD (2020). eChemPortal. Retrieved 2020-09-21 from <https://www.echemportal.org/echemportal/>

⁸ European Chemicals Agency (2020). Information on Chemicals. Retrieved 2020-09-21 from <https://echa.europa.eu/information-on-chemicals>

may be used for hazard and risk assessors globally and for regulatory purposes. More information is provided in chapter 7.5.

Test data may be required by national law for all or certain types of chemicals (e.g. pesticides). In legislation, it can be made clear that producers and importers bear the responsibility for testing substances before they are placed on the market, unless sufficient data already exists.

To understand and correctly interpret the results of testing, it is important to understand how the testing was performed. The use of internationally accepted and validated methods makes interpretation easier and facilitates exchange of information between countries. Therefore, it is advisable to base any requirements on testing on such standard methods.

*The OECD guidelines for the testing of chemicals*⁹ are internationally accepted as standard methods for testing the potential effects of chemicals on human health and the environment. They are split into five sections; physical-chemical properties (section 1), effects on biotic systems (section 2), environmental fate and behaviour (section 3), health effects (section 4) and other test guidelines (section 5). The specific guidelines developed to assess health effects are mainly based on testing in animals (in-vivo testing) but increasingly larger efforts are spent on developing non-animal testing systems. These include not only biological systems such as tissues or cells in culture (in-vitro testing) but also non-biological systems including computer modelling (e.g. (Quantitative) Structure Activity Relationships; (Q)SAR). In addition, epidemiological data, and experience of the effects on humans can be used for hazard identification, such as occupational data and data from accident databases (e.g. from poison information centres), when health hazards are evaluated.

3.1.2 Classification of hazard

The substance or mixture can be classified based on the type of the identified hazard according to generally accepted criteria. The need for a common, globally acknowledged hazard classification and labelling system for chemical substances and mixtures was highlighted already at the 1992 United Nations Conference on Environment and Development (Agenda 21)¹⁰.

The Globally Harmonized System of Classification and Labelling of Chemicals (GHS)¹¹, has been developed within the United Nations framework and the first printed edition (the “Purple Book”) was published in 2003. The GHS includes criteria for classification of substances and mixtures by type and severity of hazard. It contains internationally harmonized criteria addressing physical, health and environmental hazards.

The *hazard class* describes the type of hazard. The 8th revised edition of the GHS contains 17 physical hazard classes, ten health hazard classes and two environmental hazard classes (Table 1).

⁹ OECD iLibrary (2020). OECD Guidelines for the Testing of Chemicals. Retrieved 2020-09-21 from https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals_72d77764-en

¹⁰ United Nations Sustainable Development (1992). United Nations Conference on Environment & Development. AGENDA 21. Retrieved 2020-09-21 from <https://sustainabledevelopment.un.org/content/documents/Agenda21.pdf>

¹¹ UNECE (2020). About the GHS. Retrieved 2020-09-21 from http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html

Table 1 Hazard classes in the GHS 8th revised edition

PHYSICAL HAZARDS	HEALTH HAZARDS	ENVIRONMENTAL HAZARDS
2.1 Explosives	3.1 Acute toxicity	4.1 Hazardous to the aquatic environment
2.2 Flammable gases	3.2 Skin corrosion/irritation	4.2 Hazardous to the ozone layer
2.3 Aerosols and chemicals under pressure	3.3 Serious eye damage/eye irritation	
2.4 Oxidising gases	3.4 Respiratory or skin sensitisation	
2.5 Gases under pressure	3.5 Germ cell mutagenicity	
2.6 Flammable liquids	3.6 Carcinogenicity	
2.7 Flammable solids	3.7 Reproductive toxicity	
2.8 Self-reactive substances and mixtures	3.8 Specific target organ toxicity — single exposure	
2.9 Pyrophoric liquids	3.9 Specific target organ toxicity — repeated exposure	
2.10 Pyrophoric solids	3.10 Aspiration hazard	
2.11 Self-heating substances and mixtures		
2.12 Substances and mixtures which, in contact with water, emit flammable gases		
2.13 Oxidising liquids		
2.14 Oxidising solids		
2.15 Organic peroxides		
2.16 Corrosive to metals		
2.17 Desensitized explosives		

Each hazard class is divided into *hazard categories* that differentiate the hazard according to severity of the effect (hazard characterisation) or strength of the evidence.

It is important to stress that regardless of the use situation, the intrinsic hazard of the chemical is the same and thus the hazard assessment from one country can be of use in another country.

The OECD's eChemPortal referred to above provides classification results according to the GHS, as well as information on available national/regional hazard classification schemes.

The GHS thus provides a harmonised system for classification of hazards, but the purpose is wider and GHS also proposes harmonized communication elements, such as labels and safety data sheets. It aims to enhance the protection of human health and the environment during the handling, transport and use of chemicals. The GHS thus provides a basis for harmonization of rules and regulations on chemicals at national, regional and worldwide levels, an important factor also for trade facilitation.

While governments, regional institutions and international organisations are the primary audiences for the GHS, it also contains sufficient context and guidance for those in industry who will ultimately be implementing the requirements which have been adopted.

3.2 Hazard characterisation

In the present context, hazard characterisation is a quantitative description of the intrinsic property of a chemical having the potential to cause adverse effects. It is also referred to as dose-response assessment.

Box C Fundamental concepts relating to dose

The *dose* is defined as the total amount of a substance administered to, taken up, or absorbed by an organism, organ, or tissue.

The *dose-effect* relationship describes the association between the dose and the magnitude of a measured biological change either in an individual or in a population.

The *dose-response* relationship describes the association between the dose and the incidence of a defined biological effect in an exposed population, often expressed as a percentage.

One purpose of the hazard characterisation step is to identify a numeric value that can be used as a reference value when exposure is considered in the risk characterisation step.

At low doses, there may be no response but at some dose level a response is seen in a proportion of the exposed study population. Both the dose at which a response begins to appear and the rate at which the response increases with increasing doses differs between different substances, individuals, exposure routes, etc. Thus, the shape of the dose-response curve, which reflects the potency of the chemical, is different, depending on the substance, the kind of response and the type of exposed population.

Reference values derived from test data usually involve the use of assessment factors (AF) to consider e.g. variability between and within species and duration of the study (see Box D).

Box D Assessment factors

Assessment factors are applied to test data in order to take into account:

- *Interspecies variability* (possible differences between test animals and humans or between environmental test organisms and a whole ecosystem)
- *Intraspecies variability* (variations in sensitivity within the population)
- Exposure duration in the study
- Sensitive groups within a population
- Sensitive stages in the development of an organism
- Quality and quantity of test data

3.2.1 Health hazard characterisation

For health hazards, a distinction is made between effects that have a threshold and those that are assumed to be without a threshold.

Threshold effects

For most adverse effects, it is assumed that chemicals show a *threshold* value below which the adverse effect does not occur. Regulatory efforts are generally made to keep exposures

below the population threshold, which is the threshold of the most sensitive members in the population.

The adverse effect that occurs at the lowest dose, or in the most sensitive test species in the case of environmental assessment, is selected as the *critical effect* and applied in the risk assessment. The underlying assumption is that if the critical effect is prevented from occurring, then no other more serious effects will occur. It is important to examine all available toxicological studies for as many kinds of effects or endpoints as possible. Some of the studies (key studies) will usually be considered more important and robust than others and these studies will provide more reliable information on the critical effect(s).

The *No-Observed-Adverse-Effect-Level* (NOAEL) is the highest exposure level at which no statistically or biologically significant increases are seen in the frequency or severity of adverse effects, comparing the exposed population and its appropriate control population (Figure 1). In an experiment with NOAELs for several different endpoints, the regulatory focus is normally on the lowest one. In cases where a NOAEL has not been demonstrated experimentally, the *Lowest-Observed-Adverse-Effect-Level* (LOAEL) is used, which is the lowest tested dose where adverse effects are observed.

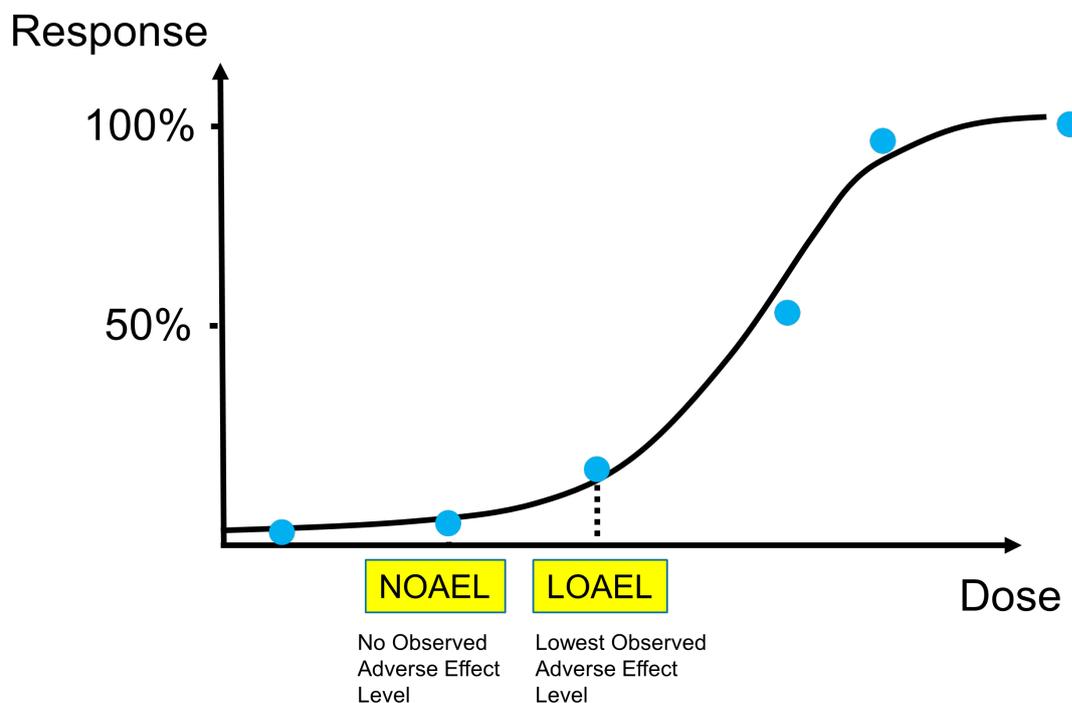


Figure 1 Schematic dose-response curve, indicating the concepts NOAEL and LOAEL

Alternatively, mathematical modelling can be used to determine the so-called *Benchmark Dose* (BMD) using several data sets. A predetermined change in the response rate of an adverse effect is selected, such as 10% increase in body weight or a 10% increase in the incidence of cancer in test animals in a long-term study. The *Benchmark Dose Lower-confidence Limit* (BMDL) is the statistical lower confidence limit of the dose that produces the selected response. This is illustrated in Figure 2.

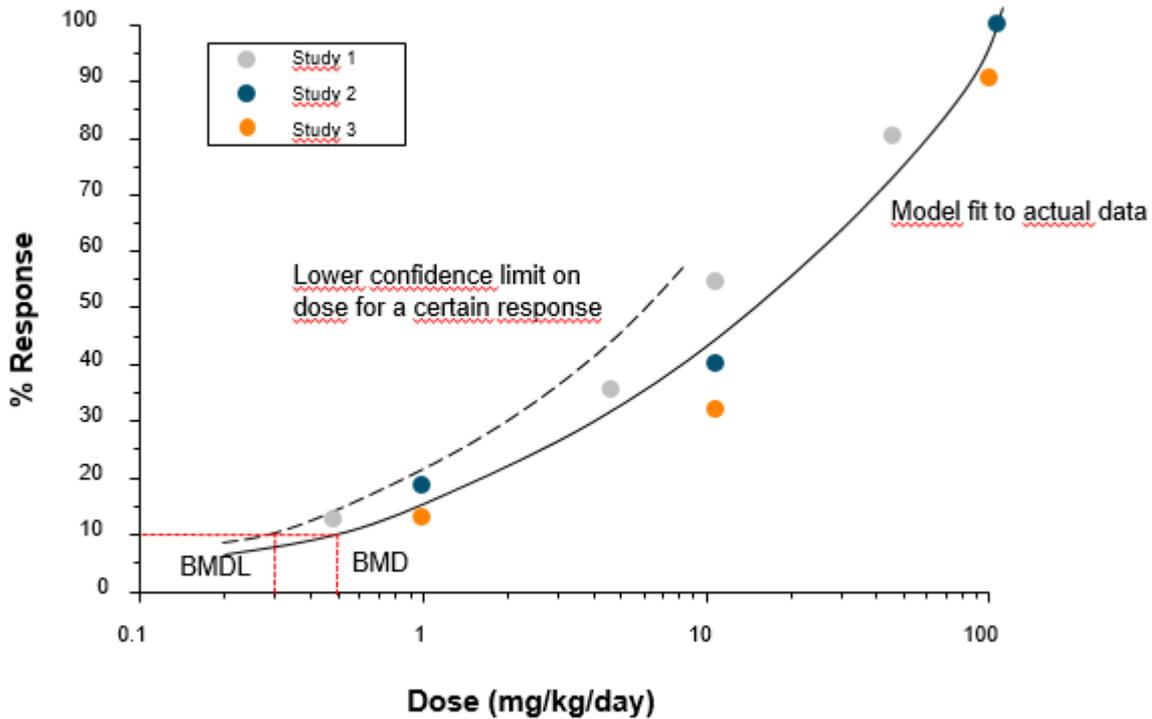


Figure 2 The Benchmark dose concept using data from three different studies.

The dose descriptors (such as NOAEL, LOAEL, BMD) can be used to derive a reference value for use in the health risk assessment. The dose is generally derived by dividing the value of the dose descriptor by assessment factors (AF)¹². The reference value is called *Derived No-Effect Level - DNEL* in EU legislation.

$$DNEL = \frac{NOAEL}{AF}$$

As mentioned above, the purpose of the AF is to take into account variability among relevant species and populations, as well as uncertainties in the data (Table 2).

Table 2 Examples of assessment factors (AF) used in EU.

Assessment factor (AF) accounting for:		Default value
Interspecies differences	rat to human	10
Intraspecies differences	Worker	5
	General population	10
	Children	10-100
Exposure duration	A larger AF is used if the data comes from a study of short duration	2-6
Dose-response	e.g. LOAEL to NOAEL	3-10
Quality of whole database		1-10

¹² other terms used are uncertainty factors, safety factors or adjustment factors

The AFs are multiplied. In the EU a default value of 100 (10 x 10) is often used to account for interspecies and intraspecies variabilities when the general public is concerned. The choice of the AF values is largely based on policy decisions.

The establishment of reference values is the basis for the subsequent steps in risk assessment. International guideline values for chemicals are the results of comprehensive processes carried out by experts at international agencies such as the WHO and IARC. The process involves assumptions of e.g. human body weight and drinking water consumption¹³. It should be noted that these assumptions may not be directly applicable to a local context where the average body weight may be lower and the daily drinking water consumption higher.

The *Chronic Reference Dose (RfD)* or *Acceptable Daily Intake (ADI)* is an estimate of the amount of a chemical in food or drinking water, expressed on a body weight basis (usually milligrams per kilogram body weight; mg/kg bw), that can be ingested daily over an extended period of time (lifetime) by humans without appreciable health risks. In general, the RfD considers sensitive groups, such as asthmatics, pregnant women, children and the elderly. When the RfD is based on air concentrations it is called the *Chronic Reference Concentration (RfC)* and expressed as mg/m³.

The *Acute Reference Dose (ARfD)* is an estimate of the amount of a substance in food and/or in drinking water that can be ingested during a short period of time (24 hours or less) without appreciable health risk to the consumer on the basis of all known facts at the time of the evaluation. It is normally expressed in mg/kg bw.

There are also guidelines for water quality and *maximum residue levels (MRL)* in food. The MRL is the highest level of a pesticide residue that is legally tolerated in or on food or feed.

The differences in RfDs between national regulatory agencies can sometimes be very large due to the use of different studies, differences in the animals that are tested, and the selected endpoints, the use of either NOAELs or LOAELs as starting points as well as differences in the assessment factors applied. As general advice and a first step, reference values adopted by international bodies such as the WHO (drinking water, air quality), FAO (food) etc. should be used. As previously mentioned, the hazard assessment is based on intrinsic properties and should therefore be globally applicable.

Non-threshold effects

For some chemicals, notably some carcinogens and chemicals causing reproductive toxicity, the threshold approach described above may not be relevant. This is based on the ability of some chemicals to cause mutations, where even a single molecule of a *mutagenic* or *genotoxic* chemical may damage the DNA in a cell. Through cell division, this damaged cell may give rise to a group (clone) or permanently abnormal cells which may ultimately develop into e.g. a tumour or a birth defect. This single hit in a single cell means that no threshold can be identified below which there is zero risk. Any exposure will increase the likelihood of an adverse outcome.

Also, in the case of *sensitising* chemicals, allergic reactions are in most cases without a practical threshold value, since previously sensitised individuals may experience life-threatening reactions to subsequent doses even if they are extremely low.

¹³ For instance, a reference value for a health effect may assume a body weight of 60 kg and a daily drinking water consumption of 2 litres per day.

Chemicals acting on the hormone system(s) (endocrine disrupting chemicals or endocrine disruptors) may also lack a practical threshold level. The effects may be more related to when in the lifespan of an organism (embryonic or foetal stage versus adult life) the exposure occurs rather than the dose.

The dose-response for these kinds of chemicals is consequently considered to be without a threshold. As mentioned, a genotoxic event that ultimately may lead to cancer can theoretically be induced by any exposure. In this case, a linear dose-response assessment approach is applied as illustrated in Figure 3.

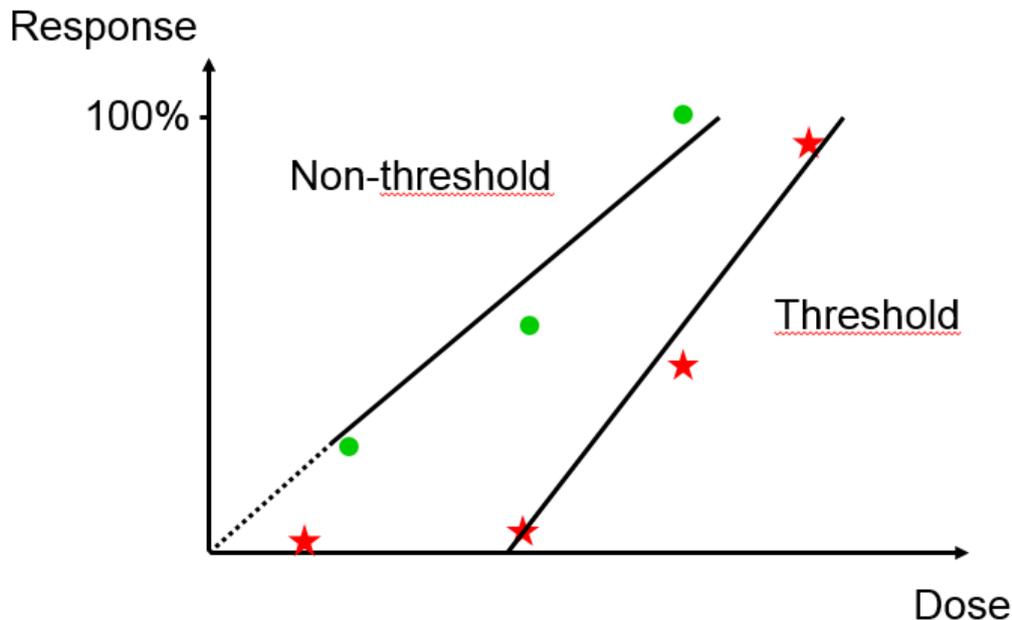


Figure 3 Illustration of non-threshold (circles) and threshold (stars) dose-response relationships.

An extrapolation is made from the relatively high doses administered to experimental animals (or exposures noted in human epidemiologic studies) to the lower exposure levels expected for general human exposure. A straight line is drawn from the point of departure for the observed data to the origin (where there is zero dose and zero response), or to the background level of an unexposed control population. The slope of this straight line is called the *slope factor* (SF).

The US EPA uses the slope factor to estimate the increased lifetime cancer risk from daily oral exposure to a chemical at a dose of 1 mg/kg bw. The oral SF can be multiplied by an estimate of lifetime exposure (in mg/kg per day) to estimate the lifetime cancer risk.

$$\text{Cancer Risk} = \text{Exposure (dose)} \times \text{Slope Factor}$$

The oral SF factor is also applied to estimate lifetime excess cancer risk upon dermal exposure to carcinogenic chemicals. In this case, the fraction of the exposure dose that is absorbed through the skin is important to consider.

For exposure through inhalation, the inhalation unit risk (UR) is an estimate of the increased cancer risk at an exposure level to a chemical at a concentration of 1 $\mu\text{g}/\text{m}^3$ for a lifetime. The UR can be multiplied by an estimate of lifetime exposure (in $\mu\text{g}/\text{m}^3$) to estimate the lifetime cancer risk.

Chemicals that act through a non-threshold mechanism are usually among those chemicals that are prioritised by authorities for regulatory action, such as bans or restrictions.

3.2.2 Environmental hazard characterisation

The objective of the environmental hazard assessment is to classify the substance regarding intrinsic hazardous properties for the environment and to determine a no-effect concentration below which adverse effects in the environmental spheres are not expected to occur.

Characterisation of environmental hazards for most chemicals primarily use data from testing on aquatic organisms from different trophic levels¹⁴, such as algae, invertebrates, and fish (Figure 4).

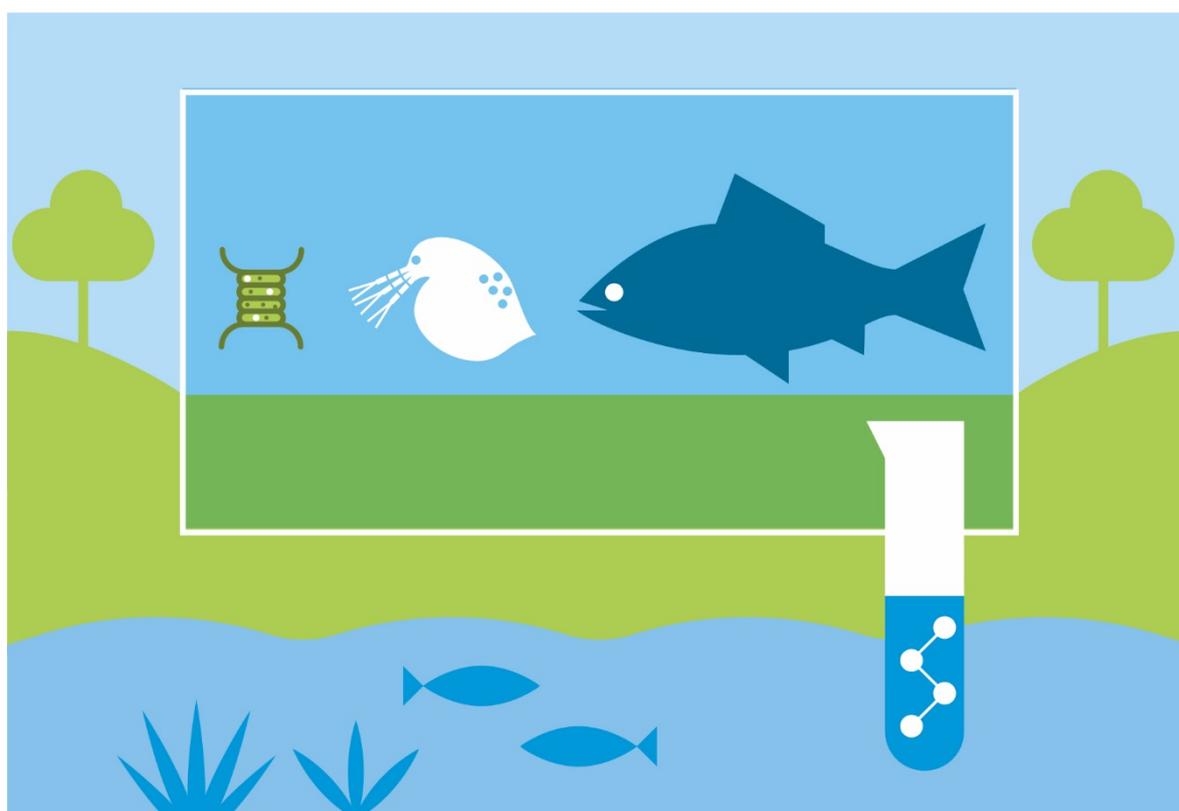


Figure 4. Test data on species from different trophic levels, algae, invertebrates and fish, is used to assess hazards from chemicals on aquatic systems. Such test data is also extrapolated to assess the hazard for other environmental spheres such as sediments and soils. Illustration: Maja Modén.

Information on aquatic toxicity is used to assess hazard and risk to freshwater organisms living in the water column. In addition, the data obtained from testing on freshwater species may also be applied for an approximate assessment of effects on marine environment as well as for extrapolation of the measured effects to other environmental spheres e.g. sediment and soil. Other target organisms used for specified testing are sediment organisms, soil organisms and wastewater treatment microorganisms. Sometimes organisms exposed via the food chain (secondary poisoning¹⁵), such as birds, are used, especially for pesticides.

¹⁴ A trophic level is the group of organisms within an ecosystem which occupy the same level in a food chain.

¹⁵ Secondary poisoning refers to the toxic effects in the higher members of a food chain that result from ingestion of organisms from lower trophic levels that contain accumulated substances.

Biotic and abiotic effects in the air compartment (atmosphere) should also be considered. However, methods for the determination of effects of chemicals on species arising from atmospheric contamination have not yet been fully developed. Therefore, the methodology used for hazard assessment of chemicals in water and soil cannot be applied yet in the same manner to the atmosphere.

The data used for environmental hazard assessment usually results from single species laboratory toxicity tests. The data is typically reported as the concentrations at which x % (e.g. 50%) mortality or inhibition of a function (e.g. growth) was observed and are expressed as the lethal concentration, LC_x , or the effect concentration, EC_x (e.g. LC_{50} or EC_{50}). The LC_x or EC_x are obtained from dose-response curves, Figure 5.

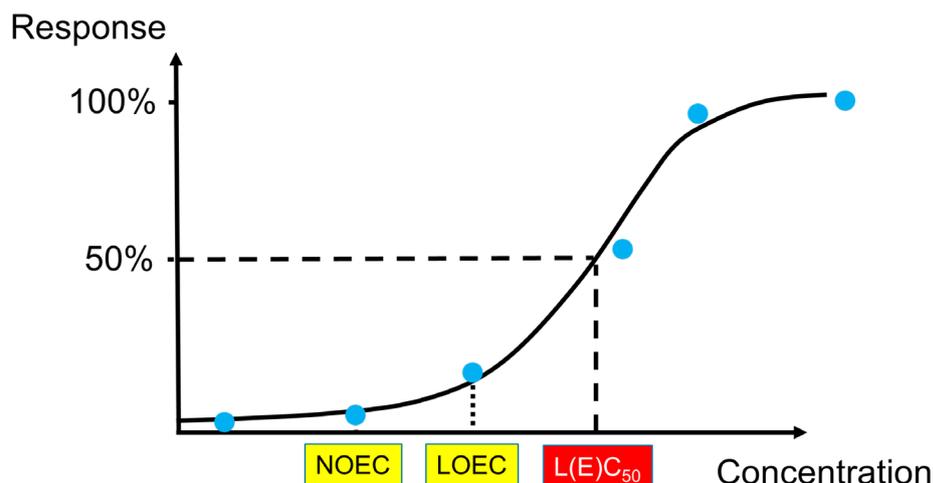


Figure 5 Schematic dose-response curve, indicating the concepts NOEC, LOEC and LC_{50} .

LC_{50} -values are usually obtained from short term tests, while the result of long term tests (e.g. reproductive success) are most frequently reported as EC_x (x being very often equal to 10) or as the NOEC (No Observed Effect Concentration). NOEC is the highest tested concentration for which there is no statistically significant difference of effect when compared to the control group. If the result is reported as a NOEC, normally also LOEC (the lowest tested concentration with significant effects compared to control) is reported.

The number of species that can be tested are limited, and since the intention is to protect the whole ecosystem, assessment factors need to be applied. For risk assessment within the EU a toxicity reference value for the environment, the *predicted no effect concentration* (PNEC), below which adverse effects will most likely not occur is calculated by applying an assessment factor (AF) to the EC_{10} or NOEC **for the most sensitive among the tested organisms**. The purpose of the AF is to consider uncertainties when extrapolating data from laboratory toxicity tests for a limited number of species to the general environment. AF applied for long-term tests are generally lower than for short-term tests (Table 3). The endpoints most frequently used for derivation of PNEC are mortality (LC_{50}), growth (EC_{10} or NOEC) and reproduction (EC_{10} or NOEC).

$$PNEC = \frac{LC_{50} \text{ or } EC_{10} \text{ or } NOEC}{AF}$$

Table 3 Examples of assessment factors (AF) applied in the EU to derive PNEC for surface water.

Available data	Assessment factor (AF)
LC ₅₀ from at least one short-term toxicity test from each of 3 trophic levels (base dataset)	1000
One long-term EC ₁₀ or NOEC from either fish, invertebrates (e.g. crustacea) or algae	100
Two long-term EC ₁₀ or NOECs from different trophic levels	50
Long-term EC ₁₀ or NOECs from at least 3 species in three different trophic levels	10

3.2.3 The PBT/vPvB concern

Substances that persist for long periods of time in the environment and have a high potential to accumulate in biota are of specific concern because their long-term effects are rarely predictable. Once they have entered the environment, exposure to these substances is very difficult to reverse, even if emissions are stopped. Therefore, the EU legislation also consider whether a substance fulfils the decision-making criteria as being persistent, bioaccumulative or toxic (PBT), very persistent/very bioaccumulative (vPvB) or a persistent organic pollutant (POP). The PBT and vPvB criteria (Table 4) are agreed by the EU member states but are not defined in the GHS¹⁶. The criteria are based on the time it takes for the substance to degrade to half of the initial concentration (T_{1/2}) in water or sediment, the bioconcentration factor (BCF), normally between water and fish, and the toxicity (EC₁₀ or NOEC).

Table 4 EU criteria for the identification of substances as persistent, bioaccumulative and toxic substances (PBT), and very persistent and very bioaccumulative (vPvB).

Property	PBT-criteria	vPvB-criteria
Persistence	T _{1/2} > 60 days in marine water, or T _{1/2} > 40 days in fresh- or estuarine water, or T _{1/2} > 180 days in marine sediment, or T _{1/2} > 120 days in fresh- or estuarine sediment, or T _{1/2} > 120 days in soil	T _{1/2} > 60 days in marine, fresh- or estuarine water, or T _{1/2} > 180 days in marine, fresh- or estuarine sediment, or T _{1/2} > 180 days in soil.
Bioaccumulation	BCF in aquatic species > 2000	BCF in aquatic species > 5000
Toxicity	NOEC or EC ₁₀ < 0.01 mg/L for marine or freshwater organisms, or substance is classified as carcinogenic (category 1A or 1B), mutagenic (category 1A or 1B), or toxic for reproduction (category 1A, 1B or 2), or other evidence of chronic toxicity as identified by the substance meeting the criteria for classification: specific target organ toxicity after repeated exposure (STOT RE category 1 or 2)	

¹⁶ However, persistency and bioaccumulation potential are included in the classification criteria for long-term (chronic) aquatic hazard.

4 Exposure

Exposure assessment determines the nature and extent of exposure for humans and organisms in the environment to chemicals under different conditions. It is the third step of the risk assessment process (see Box B) and is considered together with the hazard identification and hazard characterisation steps in the subsequent fourth step, the risk characterisation. While hazardous properties are chemical specific and data on such properties can be used globally, exposure depends on conditions that may vary between countries or, more likely, at a local level. Such conditions could be working conditions, waste management and environmental factors such as climate. Countries that are starting up activities on risk assessment of chemicals may therefore need to focus on conducting exposure assessment. However, an initial step should be to check available exposure assessments. The OECD's eChemPortal, for instance, provides links to databases on exposure and use of chemicals, with an option to search for information on a certain chemical.

The ultimate purpose of the exposure assessment is to quantitatively define a dose or concentration that can be used to estimate risk. In practice, this can be very complicated and resource demanding. As pointed out in the Swedish Chemicals Agency Guidance 2/18 on Risk reduction of chemicals, for substances with intrinsic properties giving rise to very severe or irreversible effects, it can be sufficient to base a decision for risk reduction on the hazard assessment. This could for example, be the case for substances that are:

- Persistent, bioaccumulating, and toxic (PBT),
- Very persistent and very bioaccumulating (vPvB),
- Carcinogenic, mutagenic or toxic to reproduction (CMR).

Lack of detailed, quantitative exposure data should not prevent authorities from making an estimate of the risk to the environment or human health. As a first step, it might be sufficient to base the exposure estimation on information available such as:

- Volume of the substance produced, imported, or circulated in society, either as the pure substance, as an ingredient in a mixture or in articles,
- Use pattern (e.g. whether the substance, or mixtures/articles containing the substance, is likely to be used by vulnerable populations such as children, pregnant women, illiterate persons, etc.),
- Monitoring studies or surveillance projects

If more refined exposure data exists, this information should be added or used instead.

In exposure assessments, all life cycle steps of the chemical that can lead to exposure of humans or the environment need to be considered, i.e. from production, through use, and, ultimately, disposal. Different sources may also contribute to the exposure from a chemical to one individual. The fate of the chemical in the environment as well as in the body also needs to be considered e.g. degradation in the environment as well as metabolism in the body.

An exposure assessment of a chemical should ideally include the following general steps:

- Mapping of the uses of the chemical
- Generation of exposure scenarios taking into consideration use conditions and risk management measures at the site of use
- Exposure estimation including emission estimation, assessment of chemical fate and pathways
- Quantitative estimation of exposure (dose) levels

4.1 Human exposure assessment

Regulatory exposure assessment considers the size and types of human populations potentially exposed and at risk. It is especially important to consider particularly vulnerable groups such as pregnant women, children and the elderly. Exposure data is required for the assessment of the risk due to handling and use of the substances as such but also the use of mixtures of substances as well as articles that have been treated with or may contain the substances.

Exposure (dose) assessment considers both the exposure pathways (the course a chemical takes from its source to the person(s) being exposed) as well as the exposure routes (means of entry of the chemical into the body). Exposure is usually expressed as amount per unit body weight per unit time, e.g. mg/kg bw per day.

The uptake of the chemical following exposure through ingestion, inhalation or dermal contact is followed by distribution and metabolism and finally elimination. Absorption is critical for the internal dose and ensuing systemic effects (Figure 6).

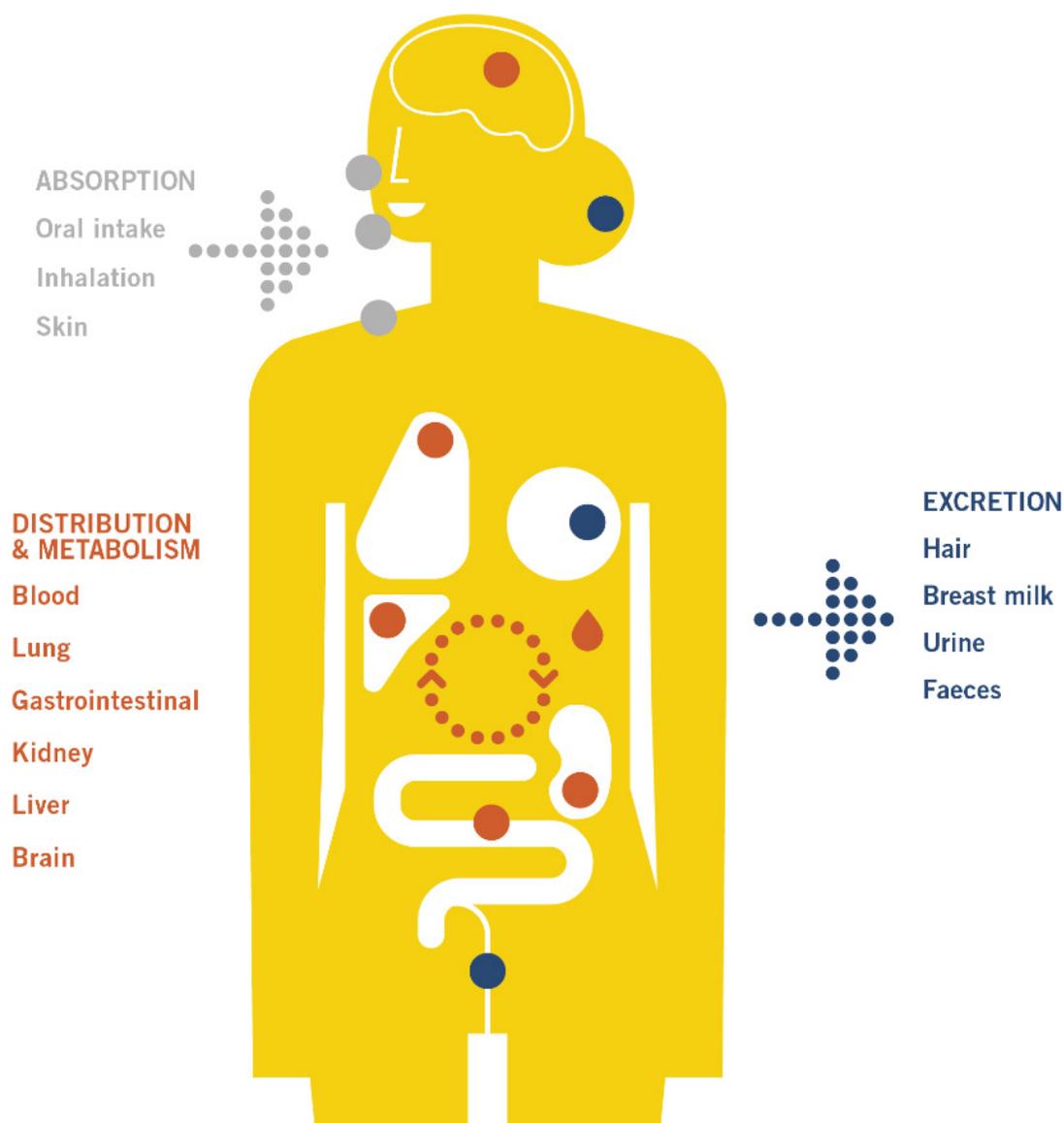


Figure 6 Schematic illustration of exposure, absorption, distribution, metabolism, and excretion of chemicals. Illustration: Maja Modén.

Exposures may be acute (one or a few exposures within hours or in a few days), sub-chronic/intermediate (repeated exposures from 14 to 90 days) and chronic exposures (up to a lifetime).

The exposure estimates and the toxicity values must be expressed in the same terms, either as administered (exposure) dose or as absorbed (internal) dose. If the reference dose or the cancer slope factor is an administered dose (intake) and the exposure estimate is an absorbed dose (uptake), or vice versa, adjustments must be made to make them comparable.

The major challenge in exposure assessment is how to relate the concentration of a substance in an external medium such as air, water, food, soil or in an article, to a dose that may result in an adverse effect.

Environmental monitoring implies sampling and analysis of a substance in environmental media (food, air, drinking water, soil, dust, etc.) that may be sources of human exposure to the substance. One example is air monitoring to assess exposure to airborne pollutants. *Biological monitoring* (biomonitoring) refers to sampling and analysis of a substance (or its metabolites)

in body fluids (urine, blood, saliva, breast milk) or tissues (e.g. fat, hair, and bone). Two examples are analysis of lead in blood and analysis of mercury¹⁷ in hair. Biological monitoring provides data on the amount of a substance absorbed via all routes of exposure and defines a total body burden. It may be possible to relate a concentration of a substance in a biological matrix (such as mercury in hair) to an external source of exposure (such as methylmercury in fish) but in most cases multiple sources of exposure exist.

Monitoring and measured data, from environmental or biological media, are valuable and highly useful but costly, need sophisticated laboratories and may raise ethical concern in the case of human biomonitoring.

A more common approach for conducting an exposure assessment is the use of *exposure models*. Many exposure models, developed both by commercial actors and governmental authorities, are available and used. For example, the website of the European Food Safety Authority (EFSA) contains tools applicable for calculation of exposure to plant protection products under different scenarios (operators, workers, residents and bystanders) as well as guidance documents¹⁸. Exposure models generally calculate exposure from a given environmental concentration using *exposure factors* such as the rate of ingestion, inhalation, and dermal contact. The models may include the use of different types of personal protective equipment, for instance when workplace exposure or pesticide application is considered. Models usually predict reasonable worst-case exposures and may include assumptions applicable to workers, consumers, and humans indirectly exposed via the environment, for instance via drinking water.

Exposure models often make use of available databases for exposure concentrations of certain substances in a specific medium under specific circumstances. International data sources, scientific literature, or governmental statistics can be used to find data on exposure factors, i.e. human (biological) characteristics (e.g. body weight at various ages), and behaviours (e.g. food consumption, drinking water intake). One example is the “Exposure factors handbook”, by the US EPA¹⁹.

The exposure is estimated by multiplying the concentration of the chemical in environmental media, such as air, drinking water or food, with the relevant exposure factors. The calculations in an exposure model rapidly become very complicated when all exposure sources and exposure routes are combined.

If exposure characteristics in the population of interest differ from the default assumptions in the model(s) used in the exposure assessment, this has to be considered. Conversely, if the focus group under consideration (e.g. children) is different from the standard population used in the hazard characterisation, adjustments have to be made. Both aspects are especially significant in developing countries, where exposures may not resemble the scenarios considered in developed countries and populations may be more vulnerable due to nutritional and disease status.

4.2 Environmental exposure assessment

Organisms are exposed to chemicals through environmental media. Ideally, exposure levels should be expressed in terms of internal concentrations at the site in the organism where the

¹⁷ reflecting methylmercury exposure

¹⁸ European Food Safety Authority (2020). Pesticide evaluation: Tools. Retrieved 2020-06-03 from <https://www.efsa.europa.eu/en/applications/pesticides/tools>

¹⁹ US Environmental Protection Agency (2018). Exposure factors handbook. Retrieved 2020-09-15 from <https://www.epa.gov/expobox/about-exposure-factors-handbook>

actual toxic effect occurs. However, lack of internal exposure as well as toxicity data based on internal doses make this impossible for the time being. Therefore, we have to base exposure assessments for organisms in the environment on external concentrations in environmental media. Hence, it is assumed that the aquatic toxicity is mainly related to the waterborne exposure of a substance and expressed as external concentration of that substance in test water. The estimated environmental exposure levels can be expressed as the *Predicted Environmental Concentration*, PEC.

Environmental exposure can be estimated through measurements (monitoring) or through computer-based modelling. Although it may seem natural to assume that measurements yield more certainty, this is not necessarily so. Chemical analyses are usually carried out on samples taken at specific locations and times. Unless monitoring programmes are designed to yield the “typical” or “average” concentrations desired in risk assessment practice, available measurements may be biased. By contrast, modelled concentrations generally do reflect the “typical” or “average” concentrations needed. Therefore, modelling may be of use in risk assessment even where taking measurements would seem to be the natural option to choose.

To estimate environmental exposure, information on the conditions of use and the related estimation of the releases to air, soil surface water, and wastewater during the whole life span (including as waste) of the chemical product is needed. It is also necessary with information on the fate and distribution of the released chemical in the different environmental spheres (air, soil, surface water, sediment, and biota) and in wastewater, treatment plants (Figure 7). Substance properties such as vapour pressure, water solubility, molecular weight, octanol-water partition coefficient, and biodegradability impact on the fate of the substance in the environment are therefore needed for the environmental exposure estimation.

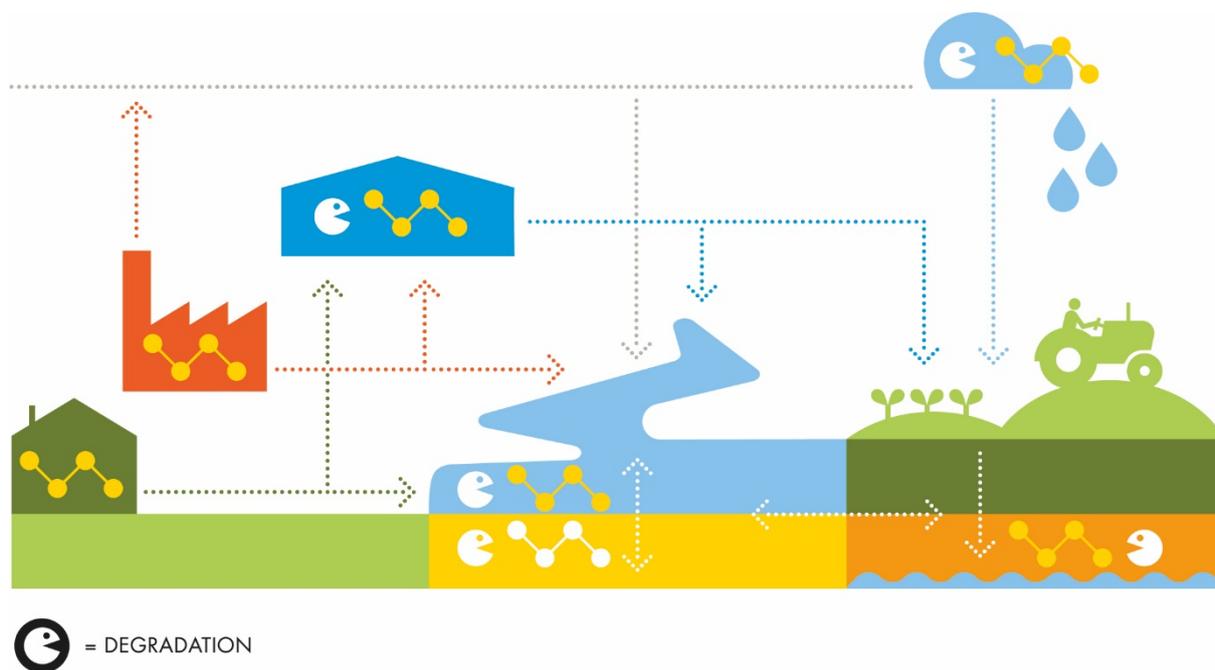


Figure 7 A chemical may reach the environment (water, air and soil) during the whole lifetime of the chemical (production, during use, as waste). The emissions may go directly to the environment or via wastewater treatment plants. The distribution of the chemical in the environment depends on inherent properties (adsorption, solubility, volatility) and the degradability of the chemical in different environments. Illustration: Maja Modén.

A variety of computer models and guidance documents for environmental exposure assessment of chemicals (calculation of exposure concentrations, PEC) are available from

various sources. Below we present the OECD-guidance on environmental exposure assessment more in detail and then shortly mention other tools for estimating environmental exposure.

4.2.1 The OECD guidance on exposure

The OECD gives guidance on environmental exposure assessment of industrial and consumer chemicals as well as biocides which it recommends making use of when making exposure assessments. This guidance is accessible for all countries, in the form of a toolkit²⁰ that refers to different guidance documents. The OECD's focus areas are:

- Release estimation.
- Exposure models.
- Use of monitoring data.

Release estimation

The OECD develops emission scenario documents (ESDs) that describe the conditions and parameters for release estimation in specific industry and use categories²¹. These are the basis for estimating the concentration of chemicals in the environment. An ESD describes the sources, production processes, pathways and use patterns with the aim of quantifying the emissions (or releases) of a chemical into water, air, soil and/or solid waste. It should ideally include all the following stages: production, formulation, industrial use, professional use, private and consumer use, service life of product/article, recovery, and waste disposal (incineration, landfill). The ESDs improve the estimation of releases of chemicals into the environment, and those related to the use of products and articles that are becoming increasingly important in risk assessment of chemicals of concern. The documents are published in the OECD Series on Emission Scenario Documents²².

Exposure models

The OECD has compiled the descriptions of existing models and tools used for exposure assessment (following the results of an OECD survey in 2010)²³. It includes a table that summarises descriptions of existing models and tools used for exposure assessment, as well as responses to the survey.

Use of monitoring data

The OECD has also published a guidance document²⁴ on exposure assessment based on environmental monitoring data. It covers topics such as:

- Environmental levels and distribution of contaminants.
- Ways of using monitoring data in exposure assessments for differing purposes.

²⁰ OECD (2013). Environmental risk assessment toolkit. See Footnote 4.

²¹ OECD (2017). Introduction to emission scenario documents. Retrieved 2020-09-21 from <http://www.oecd.org/chemicalsafety/risk-assessment/introductiontoemissionscenariodocuments.htm>

²² OECD (2019). Emission scenario documents. Retrieved 2020-09-21 from <http://www.oecd.org/chemicalsafety/emissionscenariodocuments.htm>

²³ OECD (2012). Descriptions of Existing Models and Tools used for Exposure Assessment. Results of OECD Survey. OECD Series on Testing and Assessment, No. 182. Retrieved 2020-09-21 from <http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm>

²⁴ OECD (2013) Guidance Document for Exposure Assessment based on Environmental Monitoring. OECD Series on Testing and Assessment, No. 185. Retrieved 2020-09-21 from <http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm>

- The collection of data.
- Quality of monitoring activities.
- Examples of data compilation in member countries and their use in exposure assessment.

4.2.2 Other tools for estimating environmental exposure

Within the EU there is EUSES²⁵ which is the European reference tool for companies, authorities, and researchers to prepare their environmental exposure assessments under the Biocidal Products Regulation and the REACH Regulation. Another tool is the chemical safety assessment and reporting tool Chesar²⁶. For pesticides assessment within EU there is the Forum for Co-ordination of pesticide fate models (FOCUS)²⁷. The EU models calculate PECs for soil, ground- and surface water, sediment, and sewage treatment plants. Scenarios/models are also available to calculate exposure via the food chain (secondary poisoning) e.g. to birds and mammals (including humans) through fish, invertebrates, seeds, and plants.

5 Risk characterisation

Risk characterisation combines the results of hazard identification and dose-response assessment with exposure assessment. It basically consists of obtaining the appropriate health-based guidance values and comparing these with exposure assessment data. Substance-specific toxicity information is compared against measured or estimated exposure levels to determine whether concentrations associated with an exposure are of concern and trigger risk reduction measures. Through quantitative methods, risk-assessment models estimate the probability that a specific adverse effect will occur over a wide range of doses or exposures. The level where risk reduction measures are needed should be specified in national legislation. However there are a number of internationally agreed guidelines and other documents that can serve as guidance, e.g. decision-making criteria in EU legislation or FAO criteria for “highly hazardous pesticides”.

5.1 Health risk characterisation

The inherent uncertainty in risk assessment means that risk assessors can only predict the probability of an adverse outcome. Human health risk assessments often differentiate between effects with a threshold (acute and chronic non-carcinogenic effects) and effects without a threshold (e.g. cancer).

Threshold effects

For acute and chronic effects with a threshold dose, below which the effect is not observed and for which a NOAEL or LOAEL can be determined, the exposure is compared with the corresponding reference value (such as DNEL, RfD, ADI). If the reference value is exceeded, risk reduction measures may be needed. If the reference value is not exceeded, the risk is considered acceptable, see Box E.

²⁵ European Commission (2016). The European Union System for the Evaluation of Substances. Retrieved 2020-09-21 from <https://ec.europa.eu/jrc/en/scientific-tool/european-union-system-evaluation-substances>

²⁶ Chesar (2020). CHEmical Safety Assessment and Reporting tool. Retrieved 2020-09-21 from <https://chesar.echa.europa.eu/home>

²⁷ European Commission Joint Research Centre (2020). Focus DG Sante. Retrieved 2020-09-21 from <https://esdac.jrc.ec.europa.eu/projects/focus-dg-sante>

Box E The health risk characterisation can be described as follows:

Risk unacceptable: Exposure/reference value ≥ 1

Risk acceptable: Exposure/reference value < 1

Non-threshold effects

For non-threshold effects, such as cancer with a genotoxic mode of action, the slope factor is used to derive an exposure level of low concern.

With linear extrapolations, risk is typically approximated by multiplying an exposure estimate with the slope factor:

$$\text{Risk} = \text{Exposure} \times \text{Slope Factor}$$

Risk is often expressed as how likely it is that the effect (e.g. cancer) will result from exposure to a substance. From the slope factor, or cancer potency, the dose which is associated with a specific risk level can be estimated. The risk will never be zero so a decision must be taken by authorities on a risk level that can be “accepted”. This level is often expressed as 10^{-5} or 10^{-6} , i.e. 1 extra case among 100,000 or 1,000,000 exposed.

5.2 Environmental risk characterisation

A toolkit for environmental risk assessment is available at the OECD website²⁸. In many regulatory frameworks, environmental risks are often expressed by ratios between the predicted environmental concentration, PEC, (derived from environmental exposure assessment) and the reference value, PNEC (Predicted No Effect Concentrations for the target ecosystem, derived from the toxicity testing).

When the exposure concentration (PEC) exceeds the reference value (PNEC), i.e. the ratio PEC/PNEC exceeds 1, the risk is unacceptable and risk management action is normally considered necessary. If the ratio is below 1 the risk is considered acceptable, see Box F.

Box F The environmental risk characterisation can be described as follows:

Risk unacceptable: PEC/PNEC ≥ 1

Risk acceptable: PEC/PNEC < 1

A parallel system using PEC values and NOEC values is established for pesticides. The toxicity related to the exposure value (Toxicity/ Exposure Ratio, TER) is calculated in this case. This is described more in detail in the Swedish Chemicals Agency guidance “*Hazard and risk assessment and risk reduction of pesticides*”²⁹.

²⁸ OECD (2013). Environmental risk assessment toolkit. See Footnote 4.

²⁹ Swedish Chemicals Agency (2020). Guidance on national chemicals control: Hazard and risk assessment and risk reduction of pesticides. Retrieved 2020-09-21 from <https://www.kemi.se/en/international-cooperation/guidance-for-other-countries>

6 An approach to risk assessment using available information

When conducting a risk assessment, it is important to focus on the purpose of the assessment. The assessment can be a stepwise procedure of increasing complexity and resource demand. Start simple by using a generic approach and already available risk assessment information (e.g. from international agencies or authorities and other countries). Evaluate the information to assess whether it is applicable in the local context. Depending on the needs, a more refined assessment can be made. This assessment can be focused on evaluation of data addressing the effects that most likely constitute a risk, i.e. you may not need to assess all possible effects.

Hazard identification for a specific chemical is applicable globally as it addresses intrinsic properties. International reference values are usually applicable in the hazard characterisation, but the basic assumptions made during the derivation should be considered (see section 3.2.1.).

More critically, the exposure assumptions, use patterns and environmental conditions may be different from those in already existing and available risk assessment. An initial rough estimate of the likelihood of human or environmental exposure in the country can be made by using data on quantities of the chemical on the market, e.g. import statistics, and use patterns.

For a more detailed risk assessment, some quantitative data on exposure (dose) is needed. If a realistic worst-case assumption of the exposure³⁰ in a local situation under review can be made, the results from an existing risk assessment can be used as follows:

- If an existing risk assessment shows that the risk is unacceptable and the local exposure situation is likely to be similar or higher, then risk reduction measures are needed. In this case there is no priority for further resource demanding risk assessment.
- If the existing risk assessment shows that the risk is acceptable and the local exposure situation under review is likely to be similar or lower, then the risk for the local situation is also acceptable.
- In other cases, there is a need for a local risk assessment using an exposure model and/or exposure measurements.

The different cases are summarised in Table 5.

Table 5. A bridging approach between existing risk assessments and the local situation.

Is the risk in the existing risk assessment considered acceptable?	What is the exposure level for the situation under review when compared to the existing risk assessment?		
	Higher than the existing risk assessment	Similar to the existing risk assessment	Lower than the existing risk assessment
Yes	The extrapolation is not possible: carry out a local assessment	The risk for the situation under review is acceptable	The risk for the situation under review is acceptable
No	The risk for the situation under review is not acceptable	The risk for the situation under review is not acceptable	The extrapolation is not possible: carry out a local assessment

³⁰ the highest possible exposure that can reasonably be assumed to occur

7 Risk assessment in practice – the EU example

This chapter briefly describes how hazard assessment and risk assessment of industrial chemicals are performed within the EU and provides links to resources available at the website of the European Chemicals Agency (ECHA). The guidance and recommendations for risk assessment and risk management of pesticides (plant protection products and biocides), based on information and data from the EU procedure, is separately elaborated in the Swedish Chemicals Agency guidance “*Hazard and risk assessment and risk reduction of pesticides*” (see footnote 29) .

The *EU regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals*³¹, (REACH) was adopted to improve the protection of human health and the environment from the risks that can be posed by substances, while enhancing the competitiveness of the EU chemicals industry. All substances that are manufactured or imported to the EU in volumes at or above 1 tonne/year must be registered with information on their properties and general use at ECHA. The higher the volume of a substance that is made available on the market (produced or imported), the more data is required. The basic notion is that the exposure and risk will increase as greater volumes of a substance are made available on the market.

REACH places the burden of proof on companies. To comply with the regulation, companies must identify and manage the risks linked to the substances they manufacture and market in the EU. They have to demonstrate to ECHA how the substance can be safely used, and they must communicate the risk management measures to the users.

Member States evaluate selected substances to clarify initial concerns for human health or for the environment. Authorities and ECHA's scientific committees assess whether the risks of substances can be managed. If not, authorities can restrict or ban the use of substances. The goal is that the most hazardous substances should be substituted with less dangerous ones.

ECHA has published several guidance documents relating to risk assessment (the term *Chemical Safety Assessment* or CSA is used) to support suppliers of chemicals and regulatory authorities. The guidance documents are freely available on the ECHA website³². The general procedure for a CSA is illustrated in Figure 8 and further described in the sections below. The CSA is carried out by suppliers (manufacturers and importers) to demonstrate that the risks from the exposure to a substance during manufacture and use are controlled when specific operational conditions and risk management measures are applied. These conditions of use of a substance constitute the *exposure scenario*.

³¹ EUR-Lex (2020). EU Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. Retrieved 2020-09-21 from <https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1591192516587&uri=CELEX:02006R1907-20200227>

³² ECHA (2019). Guidance on information requirements and chemical safety assessment. Retrieved 2020-09-21 from <https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment>

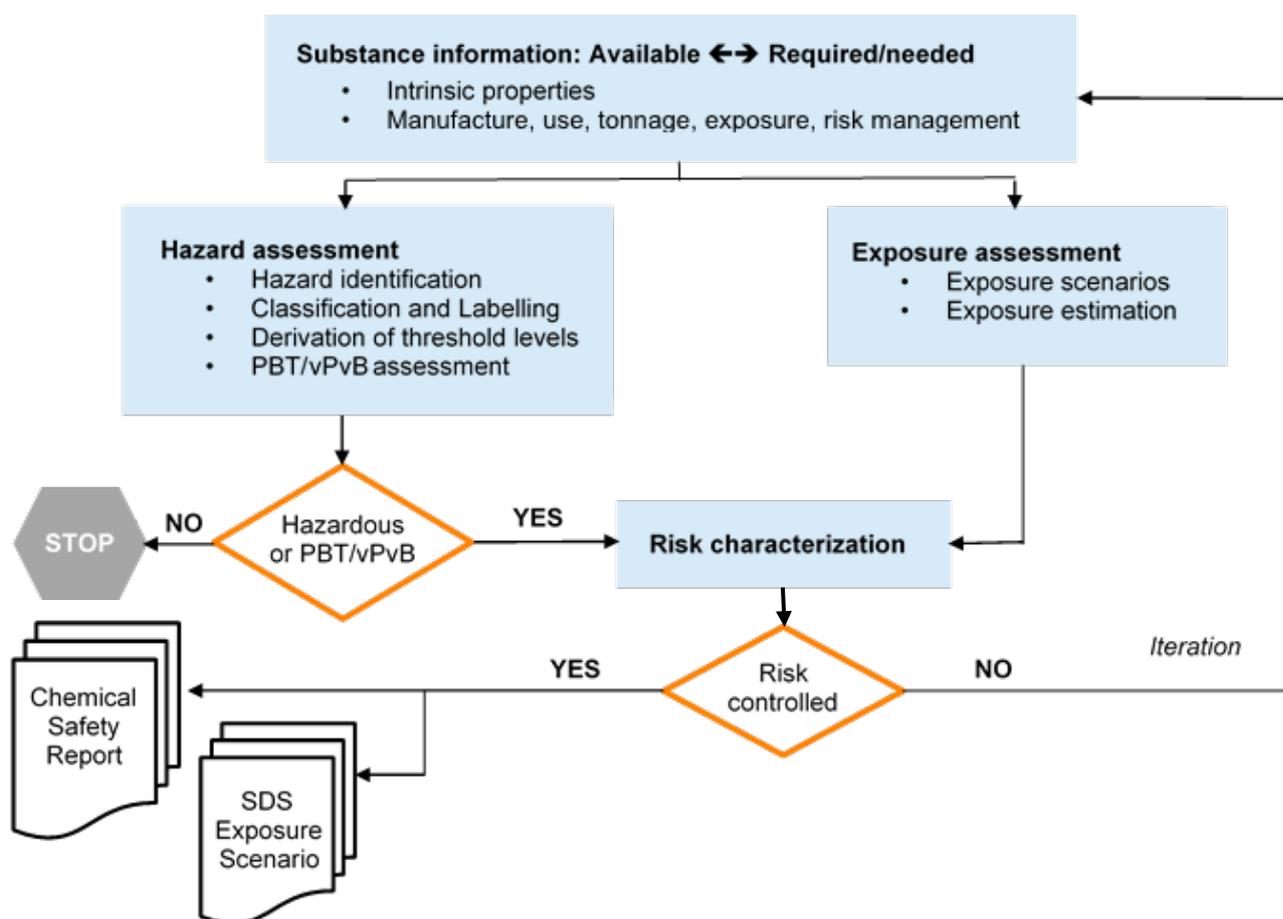


Figure 8 General procedure for chemical safety assessment according to REACH.

7.1 Hazard assessment

The CSA starts with hazard assessment, normally comprising the following steps:

- Information gathering and evaluation
- Hazard identification
- Classification and labelling
- Derivation of threshold levels (where possible)
- PBT/vPvB assessment

Based on the hazard identification, the supplier of a chemical (registrant) will define, where possible, the threshold levels for exposure below which risks for human health and for the environment are considered controlled, i.e. acceptable.

The EU system for chemicals management (REACH) requires more data for substances that are placed on the market (manufactured or imported) at higher tonnage levels. The higher data requirements include e.g. testing for more endpoints relating to human health, testing species from additional environmental spheres (soil, sediment) as well as more endpoints in environmental toxicity assessment.

7.1.1 Human health effects

The Derived No-Effect Level (DNEL) is the level of exposure to the substance above which humans should not be exposed. It is calculated by dividing the value of the health effect dose

descriptor (i.e. NOAEL, NOAEC, etc.) by assessment factors. The DNEL will vary depending on the exposure pattern to the substance and is usually defined by a combination of:

- The population likely to be exposed to the chemical (i.e. workers, consumers or humans exposed through the environment).
- The frequency and duration of the exposure (e.g. single exposure or continuous/repeated exposure for eight hours (workers) or 24 hours (general public),
- The route of exposure (oral, dermal, inhalation).

A DNEL needs to be established for each health effect and each relevant exposure pattern.

From all health effects, the lowest DNEL for each exposure pattern will be documented in the *Chemical Safety Report* (CSR) and in the safety data sheet (SDS), where required. These DNELs are used for risk characterisation.

It may not always be possible to derive DNELs for each health effect. This may be the case, for example, for carcinogenicity, where no safe threshold level can be obtained. In these cases a semi-quantitative value, known as the Derived Minimal Effect Level (DMEL) may be developed if data allows. The DMEL values represent exposure levels where the likelihood that the identified adverse effect occurs in a population is sufficiently low to be of no concern. DMELs can be used in the risk characterisation process in the same way as DNELs.

7.1.2 Environmental effects

The Predicted No-Effect Concentration (PNEC) is the concentration of a substance in any environment below which adverse effects will most likely not occur during long-term or short-term exposure. The PNEC needs to be determined for each environmental sphere (aquatic, terrestrial, atmospheric, sewage treatment, and food chain).

The lowest PNEC for each environmental sphere is reported in the CSR and in the safety data sheet, where required. The PNECs are used for risk characterisation in the CSA.

A PBT/vPvB assessment should also be carried out, using the criteria found in REACH Annex XIII. The assessment will be based on all relevant information available, including the exposure information generated in the context of the CSA.

7.2 Exposure assessment

Where the hazard assessment shows that the substance meets the CLP classification criteria as hazardous or the PBT/vPvB criteria, an exposure assessment will be required to define the levels of exposure.

The exposure assessment entails:

- Development of exposure scenarios
- Exposure estimation.

The assessment needs to cover the manufacturing and all identified uses of the substance in the whole life cycle of the substance. This will include the waste stage and, where relevant, the service-life of articles containing the substance.

7.2.1 Development of exposure scenarios

An exposure scenario is a set of information describing the conditions of manufacturing and use of a chemical substance that may give rise to exposure to humans and/or to the environment, including:

- Operational conditions (duration and frequency of use, amount of substance employed, concentration of substance in a product, process temperature, etc.).
- Risk management measures (local ventilation, air filtering systems, wastewater treatment, personal protection equipment, etc.).

7.2.2 Exposure estimation

When estimating exposure, all human populations likely to be exposed need to be addressed. Similarly, all environmental spheres for which exposure to the substance is known, need to be addressed.

In practice, the availability of reliable measured exposure data is scarce and mostly limited to a few workplaces so in most cases exposure must be estimated based on models. The two models primarily used in EU are the ECETOC TRA model³³ (for workers and consumer exposure estimation) and the EUSES model³⁴ (for environmental exposure estimation).

7.3 Risk characterisation

The exposure values will be compared with the respective reference values³⁵ (DNEL, DMEL or PNEC) in the risk characterisation. Where no reference value is available, a qualitative risk characterisation will be required.

The risk characterisation needs to be carried out for each exposure scenario in order to determine if the operational conditions and risk management measures ensure control of risks of the substance.

The quantitative risk characterisation for human health is carried out by comparing the estimated exposure level for a given exposure pattern with the lowest DNEL or DMEL value for that exposure pattern. The comparison needs to be done for each exposure pattern resulting from a given exposure scenario.

When no DNEL or DMEL is available for a health effect, a qualitative risk characterisation for that effect will be required. The purpose of the qualitative risk characterisation is to assess the likelihood that adverse effects are avoided when implementing the exposure scenario.

The quantitative risk characterisation for the environment is carried out by comparing the Predicted Environmental Concentration (PEC) with the PNEC. This is done separately for each environmental sphere, both on a local and regional scale.

When no PEC or PNEC can be derived, a qualitative risk characterisation should be conducted. This may be the case for PBT and vPvB substances for which no PNEC can be derived for any environmental sphere. The objective of the qualitative risk characterisation will be to assess the level of control over the risks generated by the substance. Operational

³³ ECETOC (2020). Targeted risk assessment (TRA). Retrieved 2020-09-21 from <http://www.ecetoc.org/tools/targeted-risk-assessment-tra/>

³⁴ ECHA (2019). EUSES - European Union System for the Evaluation of Substances. Retrieved 2020-09-21 from <https://echa.europa.eu/support/dossier-submission-tools/euses>

³⁵ The term “threshold value” is used

conditions and risk management measures will be directed to minimise emissions and exposure to the environment.

The risk characterisation will determine if the risk to humans and the environment is under control or not for a given exposure scenario.

Risk is considered adequately controlled if:

- the likelihood and severity of an event occurring due to the physicochemical properties of the substance is negligible
- the estimated exposure levels do not exceed the appropriate DNEL/DMEL or PNEC.

For substances for which a DNEL, DMEL or PNEC cannot be determined, the emissions and exposures must be minimised as far as possible, e.g. by containment. In addition, the residual risk must be low. This means that the risk is not considered to be adequately controlled. This is the case for CMRs and PBT/vPvBs when a threshold level for effects cannot be identified.

If risks are not controlled, further refinement of the CSA will be required, until the safe use of the substance can be proved or its use or uses advised against.

There are basically three options to refine the CSA process:

- *Improve the hazard assessment by obtaining more data*
If a limited toxicity data set is available it is common to use relatively large assessment factors. Additional information may lead to the use of less stringent assessment factors that account for the increased confidence in the data on toxicity.
- *Improve the exposure assessment by ensuring that the exposure estimation is realistic and reflects the conditions of use defined in the initial exposure scenario.*
Default data can be adapted or improved (e.g. including refinement of data on substance properties, emission data, exposure assumptions or other model input parameters) or by replacing modelled exposure predictions by measured data, or
- *Improve the conditions of manufacturing or use, e.g. by introducing more stringent risk management measures or changing the operational conditions in the exposure scenario.*
The operational conditions can be better described in order to get closer to reality, e.g. duration or frequency of activities. Also, the initial exposure scenario may consider implemented and recommended risk management measures.

If the residual exposure still suggests the potential for risks, stricter risk management measures need to be applied to demonstrate that the risk is controlled. In general, safer alternatives or process and technical controls should have priority over risk management measures based on the use of personal protection equipment.

7.4 The Chemical Safety Report

The chemical safety report (CSR) documents the chemical safety assessment. It also forms a basis for other REACH processes including substance evaluation, authorisation and restriction.

The CSR should be readily understandable in all its parts as a stand-alone document and it should include all the relevant information for the chemical safety assessment. The principles applied in the hazard and exposure assessments, the assumptions made, and the conclusions drawn should be transparent and well documented. The key data should be easily identifiable without the need to revert to underlying substance datasets. Professional users of chemicals

are informed on safe use through the exposure scenarios included in the extended safety data sheets.

7.5 Chemicals information available on ECHA website

As substances are registered under REACH, there is an obligation on registrants to provide information on the substances they manufacture or import. ECHA subsequently has the obligation to make certain this information be publicly available and, as a result, ECHA maintains one of the world's largest freely publicly available regulatory databases on chemical substances³⁶. The database provides valuable information that may be used for risk assessors globally and for regulatory purposes. Here you can find a variety of information on registered substances: for example, their hazardous properties, their classification, and labelling and how to use the substances safely.

The information in the folder “Information on chemicals” is available in three layers of complexity: Infocard, Brief Profile and REACH registered substance factsheet. Please be aware that ECHA does not verify the provided information before dissemination.

The amount of information provided can vary for different substances. The information comes from companies' REACH registrations, and the higher the production volume of the substance, the more information companies need to provide. Some parts of the substance information, including the chemical safety reports, are not published on the ECHA website due to confidential business information restrictions.

³⁶ European Chemicals Agency (2020). Information on Chemicals. See footnote 8

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