Exposure Scenarios in Toxicology

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Contents

Abstract

Exposure assessment represents, besides hazard identification, the second pillar that is needed for risk characterization. Exposure assessment attempts to quantify human exposures to potentially toxic substances by considering the relevant parameters: source, amount, site/place, frequency/duration, pathway/route, and

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human activity. The external exposure of the pulmonary, dermal, or gastrointestinal surfaces will – when absorption takes place – result in respective internal exposure of the organism. Exposure scenarios use the best available parameter information and apply it to a specific problem, e.g., an increased indoor air concentration of a solvent, to estimate the potential risk for different populations, such as children or aged people, taking behavior and anthropometric data into account. Deterministic and probabilistic models for quantitative exposure estimates are in use. Variability and uncertainty should be taken into account. The basics of this methodology and regulatory aspects are described in this contribution.

Keywords

Risk characterization · Exposure source · Exposure pathway · Exposure route · External exposure · Internal exposure · Exposure scenario · NOAEL · Exposure modeling · Exposed population

Introduction

Exposure is defined as the

> concentration or the amount of a particular agent that reaches a target organism, system, or (sub)population in a specific frequency for a defined duration. (WHO/IPCS 2004)

Exposure can be understood as dose estimation, by the oral, dermal, or inhalation route and is normally characterized by means of exposure scenarios. The information from the exposure scenario is needed for building up an exposure model. Exposure models can be understood as a translation of an exposure scenario to a mathematical algorithm to yield a qualitative and a quantitative estimate of exposure.

Exposure assessment is based on three basic elements: (i) the exposure scenario, (ii) the exposure model, and (iii) the exposure parameters[1] (WHO/IPCS 2005). The basic characterization of the exposure is made by the exposure scenario (ES). The ES describes the circumstances of exposure, covering all situations and corresponding information needed to perform an exposure estimate. The WHO (2004) defines the term exposure scenario as

> a combination of facts, assumptions, and interferences that define a discrete situation where potential exposures may occur. These may include the source, the exposed population, the time frame of exposure, micoenvironment(s), and the activities. Scenarios are often created to aid exposure assessors in estimating exposure.

This definition should be used as a basic concept for exposure estimation.

Since 2006, an additional definition of exposure scenario must be taken into consideration regarding to the European Chemicals Regulation (REACH; European Commission 2006). In the regulation, the exposure scenario is defined as

> . . .the set of conditions that describe how the substance is manufactured or used during its life-cycle and how the manufacturer or importer controls, or recommends others to control, exposures of humans and the environment.

This definition is basically not different to the above one, but its focus is the characterization of the measures to control the exposure and the measures to reduce it, where needed.

This chapter is explaining the exposure scenario on the basis of the WHO definition, with hints of the particularities of the REACH regulation.

Similar to drug treatment, an exposure estimate can be understood as the dose of a contaminant or hazardous substance that can be taken in by an individual or a population.

Structure of Exposure Scenarios

Exposure scenarios describe the complex characteristics of the external exposure from any substance that can be released from a variety of sources, e.g., the environment, consumer products, food, and other sources. The resulting external "dose" will be systemically absorbed and results in the toxicologically relevant "internal" exposure. The characterization of the exposure scenario describing external exposure should be divided into several parts to be combined with each other yielding the complete scenario. The different elements of an exposure scenario are broadly characterized in Heinemeyer (2019a) as shown in Fig. 1.

In the REACH regulation (European Commission 2006), the scenario contains basically the same information. However, its focus is on the information which measures are considered by the producer of the product to control the exposure to an extent that will not exceed the derived no-effect level (DNEL). If, for example, in an

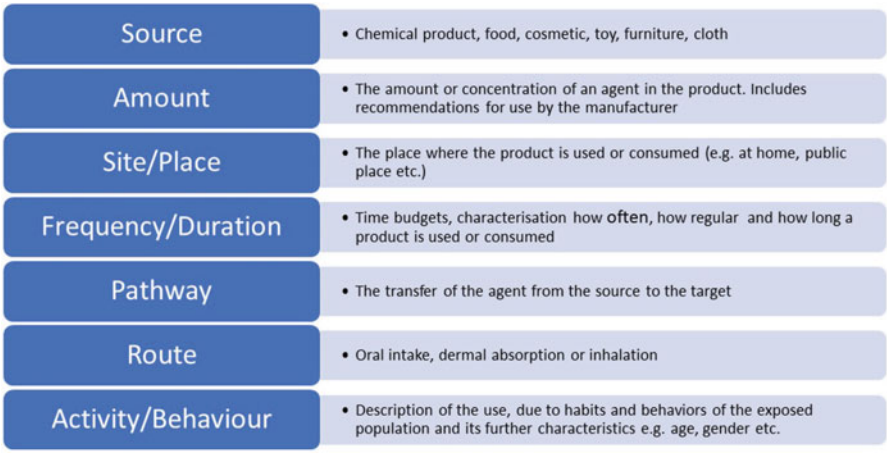

Fig. 1 Elements of an exposure scenario

exposure calculation, the DNEL is exceeded, the registrant[1] must implement measures to reduce the exposure by risk management measures (Bruinen de Bruin et al. 2007). Examples for RMM are reduction of the concentration of a substance in a product, hindrance of migration of a substance from an article, or release reduction by special dispensers. Non-exceedance of the DNEL indicates that a product is safe.

A scenario can be characterized by three parts (subscenarios). There may be an overlap of the above-shown elements of the scenario.

The first part of the exposure scenario describes the source of the substance of interest. This source may be a chemical product, food or any other products used by consumers or workers. Water, air, and soil may also serve as source. This subscenario covers information about the amount of an agent in that source that will be potentially released. The kind of the source also determines frequency and the duration of the release.

Example
A certain household cleaner (source) containing a substance in a particular concentration will be applied to a bigger area (e.g., the ground of a room) and released during and after application.

The second part of the exposure scenario describes the release and transfer from the source (pathway of exposure) and its contact and with the exposed person and the following intake/absorption (route of exposure).

Example
The substance, due to its vapor pressure and molecular weight, will be released and evaporated to room air to yield a certain concentration. The concentration will increase and continue over time and can be inhaled by persons in that room. Due to air exchange, the concentrations in room air will decrease. Substances having low volatility will be distributed mostly via the house dust path.

The third part of the exposure scenario describes the use, due to habits and behaviors of the exposed individual or population. This includes the information about activities of people using that products The frequency and duration of the actual use (working with a product, eating food, etc.*) is considered. The information is often scarce and thus is mostly characterized by default values.*

[1]Registrant: The company that prepares the chemical safety report for notification to ECHA (European Chemicals Agency)

Example 1
The exposed person stays in that room for a certain time and will inhale the air. The time an exposed person is spending in a room may account for, e.g., 4 h.

Example 2
An individual or a population eats a combination of food over a certain time period and with different frequencies.

Characterization of the Source and the Use of the Substance in a Product

This subscenario is used to characterize the source of the substance and the amount that is potentially released during the use of the product. The limitations of these processes are determined by the product itself that contains the substance, its physicochemical properties, its concentration, and the mode of use.

Categories of Use

A substance may appear as an ingredient in many different products and product types (Heinemeyer and Hahn 2005). An approach that characterizes product use categories can therefore be very helpful to identify the sources of substances. Product categories have been used on the national and international level. Some of the documents became "official" due to their use in technical guidance documents (ECHA *2010*) or from use and recommendations by international agencies (EFSA 2009) and organizations (WHO *2005*). Therefore, they have some standardizing character, although the details are differing. Major importance is due to the guidance documents and classifications used in international databases, such as the *industrial categories* and *product and article categories* described in the ECHA guidance R12 *use descriptor system* (ECHA *2010*) (Table 1).

The impact of classification of products has recently been described by Heiland (2019). Also, poison centers around the world are using product use classification systems for documentation of cases and to prepare annual reports. In most of the classification systems, a differentiation is made according to the use of the products, e.g., paints, household cleaners, pesticides, cosmetics, and others. Due to these documentations, it can be checked how close exposure scenarios are close to reality (Heinemeyer and Hahn 2005). The identification of use of a substance and the description of manufacturing and the use process is an important part in defining exposure scenarios under REACH (van Engelen et al. 2007; Heinemeyer 2008).

Table 1 Important sources of information on classification systems to characterize exposure scenarios

Reference	Editor	Remarks
AUH report	Behörde für Arbeit, gesundheit und Soziales, Hamburg. **A**usschuss für **U**mwelt**h**ygiene der AGLMB	Food intake data from the national survey 1985–1989
Bundeslebensmittelschlüssel	BVL (2012a) and Max-Rubner Institut (2012)	Nutrient database with food category system, national, Germany
Food contamination surveys	For example, BVL (2012), EFSA (2009)	
EFSA concise food consumption database	EFSA (2012)	A collection of national food consumption data due to harmonized food grouping
EFCOSUM report	Efcosum Consortium (2001), Brussard et al. (*2002*)	Report from an EU research project
LanguaL	Møller and Ireland (2010)	
EIS-Chemrisks	EU Commission, Joint Research Centre, Ispra	Project report and database EIS–Chemrisks
GEMS food	WHO (2012)	Worldwide classification system for foods
ECHA technical guidance document R12	European chemicals agency (*2010*)	Compilation of different product and article categories and product use classification for REACH
EU commission	Technical guidance document 2003	
General factsheet	RIVM; Bremmer et al. (2006a)	Collection of exposure defaults and assumptions
Paint products factsheet	RIVM, Bremmer and van Engelen (2007)	Collection of model parameters for paints
Pest control products factsheet	RIVM, Bremmer et al. (2006a)	Collection of model parameters for pesticides
ECETOC TRA	European center for ecotoxicology and toxicology of chemicals, several versions (*2012*)	Guidance document and tools for targeted exposure assessment
Annual reports of poisonings reported due to chemical law	Federal Institute for Risk Assessment (2011)	Product classification developed on national levels in cooperation with poison centers
INTOX	WHO (2012)	Classification developed for poison center annual reports

The development of classification systems available for foods is more advanced than those for other products mentioned above. Food classification was developed since longer times for systematic characterization and for nutrition evaluation, e.g.,

for food consumption surveys. The data are also used for exposure assessments. In the EU, the European Food Safety Agency (EFSA) has introduced a harmonized food classification characterization in its *Comprehensive Food Consumption Database* (EFSA *2012*), which comprises data on food consumption from nearly all EU member states. In Germany, the *Bundeslebensmittelschlüssel* (BVL *2012a*; Max-Rubner-Institut 2012b) is used to classify food. The Max-Rubner Institute is responsible to maintain this classification system up to date which is close to the *LanguaL* (Møller and Ireland 2010). The latter combines a fixed three-level thesaurus with relational and dynamic tables, so-called facets. Product/use categories can be transferred and expressed as subscenarios on different levels of aggregation to apply a standardized approach (use model) with respective exposure (model) parameters. Food classification is also extensively described by Fabiansson (2019).

Release, Distribution, and Disappearance

As in pharmacokinetics, this part of the exposure scenario describes the appearance, distribution, and disappearance of a substance in an environment. This subscenario regards mainly for exposures via the air and inhalation. It includes:

1. The description of the concentration of the substance (as described above) in the product and its release, by migration, evaporation, or emission.

2. The distribution of the substance in the surrounding environment to which emission occurs, either bound to particles, e.g., house dust, or in the gas phase.

3. The disappearance of the substance from the environment.

Source, (micro)environment, and substance characteristics are limiting the release of the substance. In combination with the use, the route of exposure will be oral, dermal, or by inhalation. In some exposure scenarios, source, pathway and route are characterized by one process, e.g., exposure via food consumption.

Exposure by Inhalation

The scenario characterizing the exposure by inhalation normally describes the concentration – time course of a volatile substance in the indoor air, either in one or multiple rooms. The concentration can be used for comparison with toxic concentrations.

It is recommended to use the concentration in air to estimate the uptake of a substance via the lungs to the systemic circulation by using the inhaled air volume and an absorption factor. Internal exposure evaluation enables risk assessors to

estimate total body burden, e.g., in children or other particular populations. To perform these estimates, the respiratory volumes per time and pulmonary absorption rates are needed.

In addition to inhalation of substances in the gas phase, the inhalation of small particles should be also taken into account. Dust is a vehicle for nonvolatile substances that can be adsorbed and desorbed from the particles, absorbed through the alveolus, and thus enter the human body.

Exposure parameters needed to estimate exposure from inhalation

- Concentration of the substance in room air
- Concentration of the substance associated with fine dust particles
- Migration rates (release rate per time)
- Vapor pressure
- Molecular mass
- Density
- Product amount used in the application
- Concentration of the substance in the product
- Duration of the application
- Room volume
- Air exchange rate
- Inhalation volume per time
- Absorption factor

Typical Scenarios of Inhalation Exposure

1. Use of volatile substance, e.g., solvents in paints, laquers, or cleaners

A certain amount of a product (e.g., a paint or cleaner) will be applied to a surface. A volatile substance will be evaporated and produces indoor room concentrations. The substance distributes in the room and disappears after some time, according to the air exchange rate. This type of scenario has been considered, e.g., in the computer tool ConsExpo (RIVM 2017) and the wall paint emission model published by the US EPA (*2001*).

2. Emission from solid bodies

A constant amount will be evaporated over a longer time period from, e.g., furniture and textiles. This may lead to constant (steady state) concentrations of the substance in indoor air. The extent of this concentration depends on the air exchange rate, temperature, and other factors, e.g., whether the substance can be adsorbed to particles. This scenario may be applicable for exposures from inhalation due to solvent contaminated residual wastes.

3. Inhalation of dust

Dust inhalation represents a special form of exposure by inhalation. By this pathway, inhalable fine particles from the microenvironment that can adsorb substances enter the lungs and alveolus. After desorption from the particles, the substance can be absorbed to the systemic circulation. Sometimes, they can remain in the alveolar cells and lead to local effects, as particles as well. The concentrations in the dust cannot be estimated and have to measured.

The example shown below represents an estimation of exposure for a child (bodyweight (BW) 8.10 kg). This estimate is characterized by its conservatism, taking low body weight (fifth percentile), a respiratory volume (RV) that considers (partly) activity *and* rest, as well a maximal contact time (CT) and a high pulmonary absorption rate (RPA; 100%). This approach is often called "worst case."

Example: Conservative Estimation of Exposure by Inhalation

- Concentration in room air (estimated or measured, C) – 10 μg/m ^{3}
- Body weight (BW) – 8.1 kg
- Respiratory volume per time (RV) – 2.9 m ^{3}/day
- Contact time (TC) – 1 day
- Pulmonal absorption rate (RPA) – 1
- Inhalation exposure (absorbed amount) [C*RV*RPA*TC/BW] – 3.5 μg/kg/day

Dermal Route of Exposure

The dermal exposure estimation characterizes the amount of a substance which is on the skin and can be absorbed through the skin.

Typical Scenarios of Dermal Exposure

1. Use of cosmetic products

A product will be applied to skin; one or more substances in the product can be absorbed through the skin. In dermal exposure assessment, products that can remain on skin (nonrinse) will be differentiated from those that will be removed by washing (rinse off).

2. Use of household cleaners

The hands will be shortly put into the water that contains the washing product. Substances in that diluted product can be adsorbed to and remain on skin and may be dermally absorbed. When taking a bath, the whole body surface will be exposed.

3. Dermal exposure via air

Volatile substances in the air can come into contact with the skin and are dermally absorbed. Normally, the extent of this exposure is small.

4. Wearing textiles and contact with leisure and hobby products

Direct contact of substances from textiles or leisure and hobby products with the skin is possible by migration to the skin. The exposure surface is the part of skin that is covered by the textile or contacting the leisure and hobby product.

5. Contact with pets

Ingredients from, e.g., pesticides used for domestic animals to treat against pest may lead to dermal contact when touching pets. Children may have oral exposure after licking hands (mouthing behavior) after touching the animals.

A basic rule for estimating dermal exposure has been described in the EU technical guidance document for existing chemicals and has been taken over by ECETOC (2005) as well as in the ECHA technical guidance documents (*2015, 2016a, 2016b*). The *amount* (AM) that can lead to exposure can be estimated from the *area* (A) of exposure times an estimated *thickness of the layer* (TL) of 0.01 cm (default value) and from the *concentration* (C) of the substance in the *product* (AM = A*TL*C). In some documents, additional *absorption rates* given as percentages are used. However, it must be considered that dermal absorption is a time-dependent process. Taking percentages as rates can lead to errors and should only be applied as a default assumption, e.g., a conservative concept assuming 100% of absorption through the skin. For short contact times (e.g., shortly applied cosmetics), correction factors have been introduced that reduces the absorption rate. In general, values from 1 – (10) – 50% are used as default assumptions, with different justifications, depending on the purpose of the evaluation. For some substances, absorption constants and coefficients have been derived, due to lipid solubility (octanol/water coefficient) and molecular weight. Respective models have been established by Wilschut et al. (1995) and have been integrated into the ConsExpo tool (RIVM 2017).

Exposure parameters needed to estimate dermal exposure.

- Exposed skin area (e.g., 840 cm^2 for hands)
- (Theoretical) thickness of layer (0.01 cm; mixtures; 0.001: articles)
- Concentration of substance in the product
- Migration rates of the substance (measured)
- Absorption coefficient (derived by model evaluation), alternative: absorption rates (conservative estimates, percentages)

Oral Route of Exposure

Oral exposure characterizes the oral intake of a substance by mouth and the amount that is absorbed in the gastrointestinal tract. Oral intake is possible with food, drinking water, house dust, the mouthing behavior, and some personal care products (e.g., tooth paste). House dust and related paths are particularly important in small children. In general oral exposure estimation requires knowledge of the concentration of the substance in and the amount of the medium that is taken in.

Typical Scenarios

1. Intake of food and drinking water

A number of different sources have to be distinguished to estimate the dietary exposure to contaminants in the food chain, pesticide residues, food additives, process contaminants, substances in food packaging, and bacterial toxins and metabolic products. Process contaminants, e.g., acrylamide or MCPD, (3-Chlor-1,2-propandiol) can be formed during heating of foods.

Dietary exposure estimation is normally performed by multiplying concentration data in the food and the respective food consumption data and correction factors, e.g., for storage and preparation. Concentrations in food can be obtained from, e.g., market control measurements. However, as these data are risk oriented, there is a reason for expecting high concentrations. Systematic and representative evaluations of concentrations in food are more adequate to study dietary exposure in a population. Such data are available from, e.g., the German food monitoring system (BVL 2012). The European Food Safety Agency is establishing a system to regularly collect data of concentrations of substances in food, collected from the member states (EFSA 2011). Due to the immense number of samples needed to describe concentrations in food, approaches have been developed to reduce numbers of sample by, e.g., pooling, for example, by the concept of total diet study (TDS; Blume and Lindtner 2019).

The identification of food consumption data normally is performed by means of questionnaire studies. On the national levels, food consumption surveys have been performed in many countries, for example, the "Nationale Verzehrsstudie II" (Max-Rubner-Institut 2012a) in Germany. There are several methodological approaches by which consumption studies can be performed (24-h recall, dietary history, food frequency study, diary studies, with and without weighing the food) (Straßburg 2019). It should be mentioned that these study types have advantages and disadvantages for the particular questions asked in risk assessment, e.g., acute or chronic hazards (Lindtner and Heinemeyer (2019).

To perform food consumption studies, foods will be characterized by a food basket that contains a significant part (normally >90%) of all foods eaten. The particular foods should be classified by a systematic food group classification system (see respective chapter).

Food exposure estimation is in general performed for the general population and normal food consumers (eaters), by taking concentration and consumption data describing a central tendency (means and medians). To describe high consumers, EFSA (2008) has proposed to identify those foods that have the highest contribution to exposure and exchange the means by 95th percentiles in the estimation equation.

2. Ingestion of substances via the house dust and soil path

House dust and soil represent an important vehicle for nonvolatile substances. House dust consists of particles from several sources, e.g., soil dust, and from pollution. It contains a lot of different materials, e.g., plant pollen, mites, human and animal skin cells (dander), fibers, soil, and vapors. Substances migrate from the different materials (textiles, floor coverings, furniture, etc.) and, after release due to mechanical or thermic influence, adsorb to house dust. Partly, bigger particles may become a part of dust themselves.

The daily intake of house dust is unknown. Extrapolations from soil intake studies are normally used to estimate exposure from house dust intake. The intake of soil has been identified by means of tracer studies, taking substances that are poorly absorbed in the gut and comparing the concentrations measured in the stool with those in the soil. The AUH report (1995) recommends to take an estimate of 16 mg (median) and 110 mg (95th percentile) as standard values for house dust intake. The US EPA (2009) employs 60 mg per day as an estimate for central tendency. The extrapolation of soil to house dust may introduce uncertainties into the assessment; overestimation of exposure by house dust should be assumed. An actual overview about house dust exposure is given by Klenow (2019).

Exposure parameters needed to estimate oral exposure

- Concentrations of the substance in food and drinking water
- Consumption values for the food or drinking water, preferably related to individual body weight
- Weight
- Concentrations of substances in house dust/soil
- Default – values of house dust intake

Behavior of Populations and Individuals

Many exposed people are limiting their exposure by themselves and by their particular behavior. Studying the behavior in certain populations is essential and plays an increasing role in exposure assessment. The instructions of use will as well as the behavior of individuals and populations will influence the variability of the use and consumption of products. Two different types can be distinguished: (i) the active exposure where a person actively uses a product and (ii) the passive exposure where the exposed person is a bystander. In case of inhalation exposure, for example, the major difference between active and passive exposure is that the active person

may be closer to the source of exposure. An older version (3.0) of the ConsExpo tool is using a fictive room volume that is considerably smaller than the room to consider that situation. The indirect exposure via the environment is a particular form of passive exposure. From this perspective, eating food is passive exposure as well as being in a room and inhaling a substance that is released from furniture, while painting that furniture is active exposure.

Active and passive exposure can also be differentiated in terms of the degree of activity having impact for, e.g., exposure by inhalation. For example, the respiratory volume over time can vary from 15 m^3/day (at rest) up to 100 m^3/day (heavy work). This may lead to considerable variability in the exposure estimate and thus having impact for the risk characterization. When estimating exposure from inhalation, it is appropriate to assume a well-balanced ratio of activity and resting times.

Exposure Estimate

The aggregated (external) exposure is estimated from all external sources and via all pathways and routes of exposure.

If several agents are involved in the exposure scenario, the estimation is called cumulated exposure. Cumulated exposure is well characterized, for example, some pesticides or chlorinated dibenzo-dioxins, substance groups having some related toxicological features. Meek et al. (2011) also discuss combined exposures a situation where agents are involved having different toxic actions.

Time Budgets

As an important element of behavior scenarios, time budgets characterize the contact times of an exposed person. In case of exposure by inhalation, this is the time a person is staying in the room where the exposure takes place. Small children have normally longer contact times as adults because they may stay at home for longer time while adults are at work, outside, or at other business. This will change with school age. It is therefore of great importance to relate the time budgets to age. Data sources for time budget are, e.g., the US-EPA exposure factors handbook, the AUH (1995) report, and the RIVM general factsheet (Bremmer et al. 2006a).

Particular Age-Related Behaviors

The evaluation of behavior can be used to characterize important differences between adults and children. For example, the ingestion of soil and house dust may account for an important amount of oral exposure in small children. This occurs primarily in the toddlers, by crawling on the ground, as well as in the kindergarten, becoming less importance in the school age. Children frequently put their hand into the mouth, which is called the *mouthing behavior*. The latter has particular importance for exposure from

insecticides after treatment of pets against insects (lies, flies). Migrating substances from toys may also be relevant for mouthing. Therefore, migration rates are very important to estimate exposure. The mouthing time may vary over a big range (Groot et al. 1998; Juberg et al. 2001; Smith and Norris 2003). House dust evaluations represent an essential part of exposure assessment in children.

Exposure parameters needed to characterize a behavior scenario

- Duration of stay
- Frequency of staying
- Air ventilation
- Activities of "daily life"
- Exposure as active user or bystander
- Hand to mouth activities

Anthropometric Data

Exposure estimation needs anthropometric data that characterize the exposed person or population. Estimation of exposure by inhalation needs, according to the exposure scenario and the respective model, data about respiration rates and the lung surface. Dermal exposure evaluation requires information about body surfaces. However, estimation results are normally related to body weight. Relation to body surface is more appropriate, because body surface is correlating better with the extracellular fluid. Many substances distribute into body water, and there is also correlation between body surface and the basic metabolic rate. This is in particular of relevance when comparing results in children and adults.

Most important anthropometric data.

- Body surface and parts of body surface, e.g., hands and arms
- Body height
- Body weight
- Respiration time volume and related to activity
- Lung surface

Single-Point-Based (Deterministic) Exposure Assessments

Exposure factors can be characterized as single numerical values (deterministic approach) or as distributions (probabilistic approach). Therefore, every deterministic value represents a certain value from the distribution. An adequate exposure estimate must take into account all possible sources, pathways and routes which may result in very complex scenarios. The estimation is performed by separated estimations of the particular pathways with subsequent summation. Possible correlations of exposure paths must be considered. Also, summarizing exposure results should only be made for central tendency estimations. Results from individual conservative estimations, e.g., by using 95th percentiles or default values, should not be summarized. Consideration of conservative estimates must be performed very carefully, possibly by

addition of one conservative estimate with other averages. The European Food Safety Agency (EFSA 2008) has proposed to take the 95th percentiles of exposures contributing most to exposure, exchange them with the averages, and sum all up.

In many exposure calculations, arbitrary high values are used, in order to end up with an overestimation, without knowing the real situation. Such approaches are often lacking from reality.

Distribution-Based (Probabilistic) Exposure Assessment

When presenting exposure parameters as distributions, the bounds of that distribution may represent the entire estimation range. It is appropriate to use well characterized distributions and their statistical descriptors as a basis for exposure estimations. A check whether or not the used value can be matched with other representative values is needed. This approach will be facilitated considerably by use of modern computer tools. The total range and variability of the individual distributions will be weighted out and ends up with a distribution as result.

Probabilistic exposure modeling can be used as an alternative that considers the variability and uncertainty of the assessment that can be demonstrated by use of a probabilistic approach (Schümann 2019). Variability is characterizing the natural variation of parameters, while the uncertainty is determined by the lack of knowledge, which is often depending on data quality. For example, the body weight in the population participating in, e.g., the German food consumption study is described mostly by variability, because it is based on a representative sample from the entire population. On the other hand, the basis of data characterizing, e.g., concentrations of substances in products or food is often very poor. Therefore, these data must be considered uncertain.

Probabilistic models are formed by taking a similar general algorithm in the model but characterizing the model variables (parameters) as distributions. If the distributions are appropriately formed, i.e., the data basis is sufficient large and the values are representative for a population, the probabilistic distributions are describing the variability of the parameters. The less the number of data is and their representativeness, the more will distributions represent a mixture of variability and increasing degree of uncertainty.

Impact of Exposure Assessment

Exposure assessment represents, besides hazard identification, the second pillar that is needed for risk characterization. The margin between the quantitative estimate exposure and the N(L)OAEL) is characterizing the risk (risk characterization). It is called the margin of exposure (MOE), in earlier times the margin of safety (MOS), but both are meaning the same. The larger the MOS/MOE is, the more can the probability of risk be denied. A concern for risk is assumed if the exposure is exceeding the NOAEL. Risk can also be expressed as a ratio of the exposure dose

and the NOAEL (see resp. chapters in this book). Uncertainty factors are used in this formula to consider uncertainties, e.g., the lack of knowledge of the intraindividual and interindividual variation between animals and humans. Using the approach of tolerable/acceptable daily dose (TDI/ADI) or the acute reference dose (ARfD) the ratio should be lower than 1.

In the REACH regulation, the DNEL will be used instead of the NOAEL (compare the resp. chapter).

For these reasons it is of great importance to estimate the exposure as exact as possible. Estimates taking exposure scenarios and models are having sometimes considerable uncertainties, leading to partly extreme ranges of the exposure estimates which depend on the exactness of the description of the exposure scenario. It is essential to describe the exposure factors as exactly as possible. The approach of using conservative scenarios may lead to overestimations, resulting from rough models or taking defaults or other conservative values as model parameters. Due to the precaution principle, there is an intention to overestimate the exposure; it should, however, not result in unrealistic results. Distribution-based (probabilistic) modeling can be taken as an appropriate alternative because it considers the range of exposure factors and reveals a distribution of exposure. Taking distributions allows to consider extremes that characterize the skewness of a distribution. Ninety-fifth and higher percentiles are therefore appropriate descriptors of conservative assumptions and estimates and thus reflect "reality."

Measurements can be taken into account for exposure estimations, if they are representative for the population of interest. On the other hand, they are showing a *shot* of a particular event or situation which can hardly be transferred to a general scenario. Measurements available for, e.g., contaminants in food, in house dust, and indoor air should therefore be given attention, but they are not necessarily representative for the scenario of interest. Although there is a lot of data available for some substances, they often lack from representability and thus can be used for risk assessment only with great caution.

Cross-References

- ▶ Assessment of Background Exposure and Additional Exposure by Human Biomonitoring
- ▶ Exposure Analysis for Indoor Contaminants
- ▶ Importance of Exposure Level for Toxicological Risk Assessment
- ▶ Uncertainty Analysis in Exposure Assessment-Relevance for Toxicological Risk Assessment

Notes

1. The term "exposure parameters" summarizes the terms "exposure factors" and "exposure data" (Heinemeyer 2019)

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