Uncertainty Analysis in Exposure Assessment-Relevance for Toxicological Risk Assessment

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Abstract

Within the last decade the documentation of uncertainty has become mandatory as a necessary part of any exposure and risk assessment. A key document that is used as a framework in many regulatory approaches is the guidance document published by the WHO (IPCS) in 2008. The structure of this chapter follows the guiding principles described there, adding information from various regulatory documents. The process of an exposure assessment is structured by the definition

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of the scope of analysis, the selection of appropriate exposure scenarios for the population under concern, and the choice of conceptual and mathematical models with appropriate parameters. The evaluation of the resulting exposure calculation should support conclusions about the likelihood of exceeding health-based guidance values. The choice of parameters must cover the existing variation of all influence factors. The process should start with simplified approaches and repeated iteratively until the level of residual uncertainty can be tolerated with respect to the purpose. Each uncertainty may be analyzed at one of three tiers: qualitative, deterministic, or variance based. The identification and evaluation of the different kinds and sources of inherent uncertainty is part of the overall analysis and documentation. By this, uncertainty analysis strongly supports informed decision-making and risk communication under uncertainty.

Keywords

Biomonitoring · Limit value · Mathematical model · Regulatory toxicology · Risk assessment · Risk management · Pollution · Scenario · Variability

Introduction

Communicating the results of an exposure assessment that is based on model assumptions and numerical estimates is demanding, communicating the inherent uncertainties at the same time makes the task complex. Any exposure analysis relies on information on the concentrations of a pollutant in an exposure media, on the circumstances and the human behavior and the activities that result in contact and exposure, as well as on the transfer rates from the exposure media to the individual. Exposure increases the internal dose when the agent is transferred into and taken up by the body. Any exposure assessment includes knowledge and assumptions with respect to appropriate exposure scenarios, in relation to the models that should reflect the selected exposure scenarios and with regard to the type and quality of available data that characterizes the exposure conditions described for a population or a subgroup of concern. Risks cannot be reliably estimated if exposures are not properly characterized and, if necessary, sufficiently quantified (IPCS-WHO 2008). Any risk quantification relies on good measurement or appropriate estimates of influential variables. Since valid exposure assessment is a core element in quantitative risk assessment, any inherent uncertainty will influence the quality of results.

Risk assessment results are predictions of the frequency and severity of effects on the ground of exposure estimates. The quality of any risk assessment, and in consequence risk management and risk communication (NRC 1994), are directly dependent on the quality of the exposure assessment process. Risk reduction is often achieved through regulation, enhancement of existing rules and laws that should result in exposure mitigation. For all regulatory purposes, sufficient knowledge about exposure conditions is a basic prerequisite for characterizing subsequent risk

management strategies. For all situations which might contribute to an exposure, the possible active sources, the relevant pathways, and the behavior patterns that contribute to exposure must be identified. The role of exposure assessment is to provide information about the distribution of expected total magnitude of exposure, about the nature of the source, about the routes of exposure, and about the individuals who are exposed. Uncertainty in risk assessment is defined by IPCS (2004) as "imperfect knowledge concerning the present or future state of an organism, system, or (sub)population under consideration." The evaluation of uncertainty has in consequence both qualitative, quantitative descriptive, and prognostic aspects.

Describing the variability, e.g., over individuals (esp. age and sex groups), over exposure situations, over time, over regions, as well as over groups with different behavior and susceptibility should reflect existing differences. These differences might reflect varying contact to hazards, different substance intake or the body burden. Variability and heterogeneity refer to the natural variations (IOM 2013) in the environment, exposure paths, and susceptibility of subpopulations. They should be seen as inherent characteristics, which cannot be controlled by the exposure assessor or the decision makers. Variability and heterogeneity cannot be reduced by collecting more information, only by a stepwise selection of more homogeneous subgroups (stratification of analysis) within the evaluation process.

Uncertainty in exposure assessment refers to any lack of knowledge regarding the true value of quantities describing the real or the expected exposure. Any uncertain information used in the exposure estimation process will lower the confidence into the validity of exposure assessment results. The National Research Council (NRC 1994) stated: "Uncertainty forces decision makers to judge how probable it is that risks will be overestimated or underestimated for every member of the exposed population, whereas variability forces them to cope with the certainty that different individuals will be subjected to risks both above and below any reference point one chooses" (NRC 1994, p. 237).

Development of a Regulatory Status of Uncertainty Analysis

Within the last decade, the documentation of uncertainty as a necessary part of any exposure and risk assessment has become mandatory for accepted chemical safety dossiers in the United States of America and Europe (U.S. EPA 2001, 2019; EU 2003; ESFA 2006; ECHA 2008, 2012a, b). Other countries have adopted the approaches (e.g., MEP 2012).

A key document that is used as a framework in all regulatory approaches is the IPCS-WHO (2008) guidance document. The structure of this overview follows the outline and the guiding principles described there. The terminology is mainly in accordance to IPCS/WHO (2004, 2008), specific terms in the context of REACH are described in ECHA (2008). A glossary of terms in the field of food safety is published by EFSA (2012).

Uncertainty analysis plays a central role in risk communication. It might clarify the question which confidence should be given to the risk assessment results in total

and how the reported results might be evaluated in relation to the residual uncertainties. Since the objective of any exposure assessment in a regulatory context is contributing reliable information to the process of decision-making, all sources and all consequences of existing variability, heterogeneity, and uncertainty should be identified (e.g., Morgan and Henrion 1990; Özkaynak et al. 2008). Uncertainty analysis increases the transparency about the state of knowledge, about inherent assumptions, and about the data quality that influences the results of an assessment. The IPCS-WHO (2008) document includes ten recommendations, which summarize methods and some experience with uncertainty analysis.

(IPCS/WHO 1) Uncertainty analysis should be an integral part of exposure assessment.

The recommendation proposes that all steps from the definition of the scope of assessment, the selection of the target variables up to the summary report of the assessment should be evaluated and at least the main results of an uncertainty analysis must be part of the documentation.

Uncertainty analysis should display which information might be assumed to be sufficient reliable and which should be used with caution. Furthermore, an uncertainty analysis might clarify which steps and actions might be taken to reduce the level of uncertainty. A sensitivity analysis as part of uncertainty analysis might additionally contribute important information for the risk management process:

It will clarify which model variables (influence factors) have a high impact on the overall exposure. A comparative evaluation of the costs, the time and the necessary efforts for an increase in quality on one side and the expected information gain for the risk management process on the other side might be an additional result of such an evaluation.

An exposure and risk assessment should be organized as a stepwise process (tiered approach) that starts with a simplified approach, e.g., with simplified scenarios, simple models, and/or with defaults for reasonable upper-bound estimates for all model variables. Such screening approaches should mostly overestimate the real population exposure since it is based on conservative assumptions in terms of influence. However, the approach has the advantage of simplicity, not requiring detailed information about each variable. Using appropriate parameter values the calculation might result in an estimate with high coverage of possible exposure and risk. If no risk is identified with such a screening methodology, it is not necessary to use more sophisticated calculation tools (EFSA 2007). If the documentation of inherent uncertainties does not indicate to restrictions with respect to an interpretation of results, even such a simplified analysis might be useful for the management decision. But such simplified approaches should generate valid upper-bound-estimates of possible exposure for the population under consideration, with a low degree of inherent residual uncertainty.

(IPCS/WHO 2) The level of detail of the uncertainty analysis should be based on a tiered approach and consistent with the overall scope and purpose of the exposure and risk assessment

If the quality assessment points to relevant limitations or if the results indicate to uncertain, but relevant results, an iterative refinement of the scenarios, of the models, and of the data basis will be necessary. Under these circumstances, a refinement would be required to achieve a sufficient quality of the results.

A simplified upper-bound exposure assessment together with an uncertainty analysis might have a high value in risk communication: The management might use the preliminary results as a first and timely, but uncertain, estimate. The risk management might furthermore describe the ongoing and planned steps to clarify the exposure situation, requiring iteration. And, the exposure assessors will have a justification for a time- and resource-binding refinement of the exposure assessment on a higher tier.

(IPCS/WHO 10) Communication of the results of exposure assessment uncertainties to the different stakeholders should reflect the different needs of the audiences in a transparent and understandable manner.

Communicating uncertain information in parallel with a description of the inherent problems, joined by a statement about necessary or ongoing steps to reduce uncertainty, might have a higher degree of perceived accuracy and credibility than waiting for complete information. Giving no or restricted information to the public is communication too. If necessary, even decisions for controlling existing risks might be made on a provisional basis, subject to verification or revision. It is the responsibility of the exposure (and risk) assessment experts to explain the inherent uncertainties. Since the audiences of risk communication may differ with respect to knowledge in the field, interests, and demands, the task of explaining exposure assessment results together with an uncertainty analysis will always be difficult. A detailed analysis of uncertainties will support the risk communication process with respect to the demands, to arising individual questions, and to the general requirements.

Rationale for Characterizing Uncertainty in Exposure Assessment

The evaluation of human health risks requires information about the pollutant (e.g., emission rates, physical and chemical characterization of the substances, rates of degradation, and transformation), environmental concentrations, sources and pathways of exposure, and exposure/dose-response data. Information about each of these assessment elements might be limited. The identification of critical gaps in knowledge (scenarios and models) and data quality will be supported by a stepwise evaluation of uncertainties.

(IPCS/WHO 3) Sources of uncertainty and variability should be systematically identified and evaluated in the exposure assessment

Definition of Assessment Objectives

The assessment objectives should be clearly defined. "Which information is of most interest?" This question has to be decided together with the risk management by the risk assessor prior to any exposure analysis. Within the first phase of an assessment, the reduction of language-based uncertainty should be seen as a communication target. Precision of language is often overlooked as a source of uncertainty in this phase of the assessment (Carey and Burgman 2008), it can result in misunderstanding, lost efforts, and delay. In general, exposure assessment should provide information about the nature of the source(s) and route(s) of exposure as well as information about the individuals who are exposed (Cullen and Frey 1999). Two different purposes for exposure assessment might be distinguished, (a) to assess the safety of legal limits (e.g., preregulatory dietary exposure assessment), or (b) to assess the actual exposure situation of a population or a specific subgroup (post-regulatory exposure assessment).

For regulatory purposes a mayor question that should be answered is "Do the results indicate to exposure higher than a predefined critical limit?" This requires in general a comparison to TDI, ADI, PTWI, or DNEL values. The unit of evaluation, in general expressed as [mg substance per kg body weight for a given time scale (maximal daily, average daily of long-term exposure)] should be defined in advance. If the results of an exposure assessment indicate, even in parts, a "higher/near the evaluation level" answer, (a) those ranges of the input variables that generate high exposure or risk, (b) those subgroups which show high exposure, and/or (c) those specific sources and pathways contributing to this situation should be identified (IPCS/WHO 1994, 2005). This requires qualitative evaluation, quantitative ranking of relevant inputs variables, and a discrimination of the importance among the influence factors. By this, input variables (and their inherent variance) that do not contribute to critical results could be separated from those influence factors (variables) that contribute mostly to high exposure conditions. It is the task of the exposure assessor to clarify the influence structure together with the identification of possible error sources and uncertainties.

Typical questions of the management and the public which call for an uncertainty analysis (Saltelli et al. 2004) are: (a) How confident are you in the results? (b) How much will the results change if the basic (input) data is slightly wrong or will change over time, over regions, over subgroups? (c) Which impact any change of input data and assumptions will have? (d) Which of the uncertain input factors is most important in determining the output? (e) If we could invest in elimination of uncertainty in one of the input factors, which factor should we start with to reduce the uncertainty of results?

Once the objectives are defined, the assessment must be designed to address them. An emerging challenge is how to quantify variability and uncertainty in integrated assessments over the source to exposure to uptake continuum. Since in general many scientific fields are tangled, any exposure assessment process should be seen as an interdisciplinary approach.

Sources of Uncertainty in Exposure Assessment

The IPCS-WHO (2008) harmonization document calls for an analysis and full description for characterizing uncertainty using qualitative as well as quantitative approaches. Although inconsistencies in the application and methodology of uncertainty analysis might be seen, comparing the recommendations of different organizations, some common elements should be highlighted – these include qualitative and quantitative approaches.

(IPCS/WHO 7) Uncertainty analyses for exposure assessment should be documented fully and systematically in a transparent manner, including both qualitative and quantitative aspects pertaining to data, methods, scenarios, inputs, models, outputs, sensitivity analysis and interpretation of results.

The level of uncertainty that is contributed by the selection of scenarios, the conceptual and mathematical model applied and the choice of parameters should be documented. A qualitative evaluation should include the appraisal of the current scientific knowledge base. Controversial sources of uncertainty should be referred to and a (qualitative) evaluation of inherent subjectivity of choices for each of the controversial sources should be presented.

(IPCS/WHO 5) Data, expert judgement, or both should be used to inform the specification of uncertainties for scenarios, models and model parameters.

If different scientific approaches are available, then evidence and plausibility, the scientific support and the consistency of methods and data should be considered. The robustness of results using different assumptions and models (choice space) should be checked. By this, a full uncertainty analysis might offer a framework to facilitate and promote a qualitative consideration of the impact that uncertainties might have on the exposure assessment's results.

Scenario Uncertainty

The scenarios should describe how people may be exposed to substances by emission, by ambient air pollutants, during manufacture, during industrial, professional, and consumer use of products as well as during the service life of articles and products. In principle, all scenarios do not reflect one specific local situation, but have the objective to be representative of either mean, typical, or most sensitive situations in a region for a defined population (EC 2000). Scenario uncertainty includes possible descriptive errors (e.g., wrong or incomplete information about the facts), aggregation errors (e.g., approximations for population subgroups, time scale, season, and regional differences), errors of assessment (e.g., choice of provisional model, extrapolation from other exposure situations), and errors of incomplete analysis (e.g., overlooking/ ignoring important exposure pathways and sources).

For exposure to chemical substances, ECHA (2008) proposed some rules for considering exposure scenarios: If the intended use of a chemical is known, as it is assumed in ECHA regulations, then a detailed description of all resulting exposure scenarios is required. The type and the number of exposure scenarios depend on how the substance is used in a predicable manner. Attributes that trigger the description of exposure scenarios are the sectors of use (SU), the product category (PC), the article category (AC) together with the environmental release category (ERC). For exposure in occupational settings the process category (PROC) should characterize production- and application-related characteristics. For consumer exposure, the product categories are defined in ECHA's Guidance R.12 (2008), describing the scope of exposure scenarios.

Uncertainties might arise, (a) if the identified uses are not consistent with other sources of information, if (b) identified uses are not covered by exposure scenarios or, (c) if operational conditions do not seem to be sufficiently realistic. Within a REACH chemical safety report (CSR) the description of all exposure scenarios should ensure the safe use of the substance. The necessary control measures must be described by the manufacturer or the importer. All determinants that reflect the conditions of use and the risk management measures should be reported within the exposure scenario description. Model assumptions should be reported in the exposure tables included in the chemical safety reports (CSR).

The variability in consumer behavior and the recognition of possible multiple exposures to the same substances from different products have to be taken into account in the consumer exposure setting. Additional information about the scenario description and the assessment methods are available in the ECHA (2010, 2011, 2012b) guidance documents which includes several practical examples.

A concise description of exposure scenarios might be used as a starting point for a conceptual description how exposure might occur. Relevant exposure events might differ over age (e.g., due to behavior, consumption, sources), sex/gender (e.g., with respect to behavior like using cosmetics, product usage), and region (e.g., by nutritional habits and environmental conditions).

A valid and reliable estimation of exposure requires appropriate description of scenarios, scientific concepts to translate this knowledge in to appropriate models and adequate formulas within a mathematical model to represent the exposure scenario.

Model Uncertainty

Any mathematical model corresponding to an exposure scenario should reflect the dependencies of the degree of exposure in relation to all influential factors. The identification and description of all relevant exposure scenarios is an important prerequisite. An exposure assessment should provide full information about the origin of the model together with a detailed description and its validation status. This includes all formula(s) and a brief description of all variables. The set of involved variables needs a definition with respect to the content and the units

used. A list of all parameter values or distributions that represent the exposure factors within the population under concern should be part of the documentation. Any uncertainty that is related to the exposure scenarios will propagate to the exposure model and will influence the uncertainty of results. A general structure of exposure models includes information for each route/pathway (oral, dermal, inhalation) as well as for all exposure sources: the contact or intake frequency, the amount of transfer per contact/intake/uptake, as well as information about the concentration of the substance per item unit (e.g., mg Me Hg/kg Fish fresh weight, μg NO2/m^3 air). The total exposure is calculated as the sum over all pathways each including a sum over all contributing sources. The specific time intervals for all these intake-related variables should be defined in a homogeneous way.

$$\frac{Intake}{Time} = \sum_{i=1}^{Path} \times \left(\sum_{j=1}^{Sources} \frac{ContactFrquency_{Sources}}{Time} * Intake_{Event/Time} * Concentration_{Sources} \right) * Transfer_{Path}$$

Although the structure of the model is simple, the collection of information for an exposure model with many sources for exposure and different contributing pathways is demanding. For each pathway, at least one variable for a transfer factor is necessary. If the concentration of the substance of interest is changing in preparation (e.g., peeling or cooking/frying) or if concentration data is only available for whole food concentration then a transfer factor should describe the corresponding rate of change in concentration. If the internal (ingested/absorbed) dose is the target variable, assessing the dose within the body after the agent enters the body via ingestion, inhalation, or dermal absorption requires a transfer factor including sufficient information about the rate of absorption. The intake by each pathway (oral, dermal, inhalation) is a sum over all contact items (sources). All sources of exposure (e.g., food items, contact material, product application, indoor and outdoor immission) must be considered, as long as not at least one of the multiplication terms of the exposure equation equals (near) zero.

It should be noted that variance, measurement errors, and uncertainty of each element in the calculation propagate in a factorial manner (multiplication). The uncertainty of each source-related exposure is dependent on the quality of information of all elements in the part of model equation. The errors ε_i of each source-related intake estimate, describing the total of uncertainty for this item (e.g., the average methylmercury intake MeHg per day by tuna consumption) will increase the total error in a multiplicative manner.

The measured (or estimated) value of each parameter might be described as a composite of the true value x_i and an error ε_i, the latter dependent on the uncertainty of each variable (e.g., for the estimate of methylmercury intake by tuna the frequency of consumption, the amount eaten per meal, the MeHg concentration in fresh tuna,

and transfer factor for preparation factor and absorption rate). The type of error linkage might be additive ($V_i = x_i + \varepsilon_i$) or multiplicative ($V_i = x_i * \varepsilon_i$), depending on the variable.

$$\textbf{Total Error of intake estimate}_{\textbf{Item i}} = \varepsilon_i \sim \varepsilon_{\textbf{frequency}} * \varepsilon_{\textbf{amount}} * \varepsilon_{\textbf{concentration}} * \varepsilon_{\textbf{transfer}}$$

The error of the intake estimates of each source is the multiplicative combination of all errors. Any systematic shift or error in exposure frequency, of the amount consumed, or in substance concentration will result in an error of the exposure estimate. The sum of substance intake over all items (e.g., methylmercury exposure sources) per pathway might include many partial calculations (e.g., with varying consumption of different fish/food species with varying substance concentrations). Each might have a different quality. An exposure assessment integrates all the information about the sources and the relevant pathways into one exposure estimate. In consequence, the uncertainty analysis gains complexity. At least a basic evaluation of possible error sources is necessary to avoid wrong or distorted estimates.

The lack of quality might be a result of the model selection too. Describing an average exposure (per day, per week, per month) will require statistical information about average contacts, average frequencies, and average amounts of use, consumption, ingestion, or inhalation together with information about the substance concentration over time. A model that is describing exposure in an event-based manner requires much more information (e.g., the number of hand-to-mouth-contacts for toddlers per time unit, the contamination distribution of the contact environment over a certain period, the substance transfer by hand-to-surface-contact and by hand-to-mouth-transfer). In consequence, the time scale of the model variables and the information about the variables should be in accordance with the time scale of the target variable of the assessment.

Exposure models might describe different periods of time: The temporal scale for estimating exposure (and dose) depends on the scope of assessment. These might be peak doses (aRfD: acute reference dose), exposures occurring over a very short period of time (e.g., minutes), time-weighted averages, or exposure per day (e.g., for ADI, TDI, RfD comparison) or doses per week (e.g., for PTWI comparison). Exposure models should express the total intake for a specific time interval as the sum over all relevant pathways: e.g., dietary and nondietary intake (oral), skin contact (dermal), and inhalation.

$$\text{Intake}_{\text{total exposure}} = \text{Intake}_{\text{oral}} + \text{Intake}_{\text{dermal}} + \text{Intake}_{\text{inhalation}}$$

The errors and uncertainties of the path related intake estimates $\varepsilon_{\text{total exposure}}$ will add up over all pathways. In general, the contribution of each path to the total exposure should be documented. An evaluation of inherent uncertainty per pathway is recommended.

$$\text{Error of estimate}_{\text{total exposure}} = \varepsilon_{\text{total exposure}} = \varepsilon_{\text{oral}} + \varepsilon_{\text{dermal}} + \varepsilon_{\text{inhalation}}$$

The magnitude of exposure is in general reported as an approximation of a risk-related numerical value, the total exposure divided by the body weight (as a proxy for the distribution volume). By this, the exposure estimate and the regulatory values, e.g., for the TDI, ADI, PTWI are reported in unified units [e.g., mg substance/kg body weight per time unit]. The step of dividing exposure by body weight introduces some additional uncertainty: (a) body weights show variation, (b) the intake (e.g., water, and food consumption) might be correlated to the body weight, (c) the relation between intake (e.g., breathing volume) and age might show non-linearities and (d) the relationship between nominator (exposure) and denominator (body weight and time scale used) might be moderated by other influential factors (e.g., level of activity, cultural and nutrition habits). All these relations might result in a lack of independence of the parameters. If these influences might result in systematic over- or underestimation, correlation and dependency between variables of the model must be included into the assessment.

(IPCS/WHO 4) The presence or absence of moderate to strong dependencies between model inputs is to be discussed and appropriately accounted for in the analysis.

Good modelling approaches use sensitivity analysis as a companion tool to identify possible errors (e.g., by evaluation of predictions of the model results against known data as a model calibration). Sensitivity analysis might demonstrate the possible impact of dependencies (e.g., described by correlation between the input variables).

Parameter Uncertainty

As a starting point for a (deterministic) exposure assessment in general, default values (single-value-estimates) are used. These defaults should correspond to a description of the central tendency (mean, median of the parameter distribution representing the target population) or should stand for an upper-bound-estimate (e.g., reasonable-most-exposed (RME) in general described by 95%-distribution coverage of the particular variable. If the assessors intended as a screening step to produce conservative estimates of exposure (Hart et al. 2002), a combination of RME values for variables in the nominator (e.g., consumption per day, concentration) and lower-bound-estimates (e.g., 5%-quantiles) of the denominator (e.g., body weight) should be used for calculation. It has to be provided that the choice of a model and RME default parameters include appropriate conservative assumptions to take account for uncertainty. The Scientific Committee of the EFSA (2006, 2007) recommends that each scientific panel should review whether this requirement is satisfied by the assumptions and default values that they used previously. Treating the most significant uncertainties at each refinement step (higher tiers) progressively should refine the characterization of uncertainty about the likelihood of exceeding health-based guidance values. This should be done stepwise by evaluating the variability and the uncertainty in an integrated assessment. The numerical

description of uncertainty in parameters might be given as (a) symmetric confidence intervals (e.g., defined by standard deviations), (b) defined quantile ranges and error bands, or (c) as asymmetric confidence bands [$CI_{lower\ bound}$, $CI_{upper\ bound}$] for skewed distributions. A short justification for each selection should be given.

Uncertainty in Measurement

Ideally, any measurement informing an exposure assessment would be free of random error and should not be influenced by systematic error. The higher the quality of a measurement instrument with respect to accuracy (bias) and precision, the lower the uncertainty will be. Random error is associated with the fact that repeated measurement in general will provide different measured values although the attributes of the object are assumed to be constant over time. The term "random error" describes the unpredictability of the deviances in a series of measures. Random error of a model parameter restricts the reliability. If a numerical estimate of the random error is available (e.g., by repeated measurement→reliability), the quantitative impact of random errors on the exposure results might be evaluated directly.

Systematic errors generate shifts on the measurement scale of model parameters. They might depend on external influence factors (e.g., differences over measurement instruments, over observers, over laboratory standards, and in relation to conditions of measurement and sampling). The degree of confidence about the absence of systematic error is described in general in a qualitative manner. If the direction of a systematic error is known, but not its magnitude, then the impact on the results might be estimated only in a qualitative manner. If a systematic error might be described by numerical boundaries, then the range of a possible quantitative impact on the results might be estimated too.

The resulting one-dimensional uncertainty interval of the results might describe the range of "true" value(s) of the outcome. For a detailed description and discussion of dealing with uncertainty in measurement, we refer to references for standards of measurement (e.g., ISO 1993; ASME 2005; JCGM 2008; NIST 2011).

Exposure assessment involves the specification of numerical values for all variables which are included in the exposure model. Selecting appropriate parameters for the model's variables is a crucial factor for the model validity. But, with few exceptions the data available for an assessment will not be closely related to the exposure scenario (e.g., specific subgroups of consumers, regions) that has given rise to the request from the risk managers. In consequence, there will be always uncertainties, most of which cannot be quantified (EC 2000, p. 38) but discussed in a qualitative manner.

Data Sources for Model Parameters (Exposure Factors)

Numerical default values for exposure parameters are obtained using various approaches (e.g., expert judgement, statistical analysis) and different sources (e.g., survey data, consumer panels, market observation). Within the last years, several countries have reported National Exposure Factor handbooks. Those

collections with a longer tradition back to the 90th are U.S. EPA's Exposure Factors Handbook (for adults: U.S. EPA 2011, for children: 2008, 2009), the European Union's (EU) Technical Guidance Document (EU 2003), the German XProb project (AUH 1995; Mekel et al. 2007, UBA 2011), and the European KTL's ExpoFacts (Vuori et al. 2006; JRC 2010) and the ConsExpo Fact sheets (RIVM 2012a, b).

Adjacent to reporting default values (e.g., median, mean, upper quantiles), these documents include information about the parameters: (a) descriptive statistics including variability, (b) the cumulative distribution and in parts (c), the type of underlying distribution (EPA 1999). In general, a stratification for age and sex, and if necessary due to population heterogeneity, stratification by ethnic groups is included. "Variability and heterogeneity refer to the natural variations in the environment, exposure paths, and susceptibility of subpopulations. They are inherent characteristics of a system under study, cannot be controlled by decision makers, and cannot be reduced by collecting more information." (IOM 2013, p. 3). Statistical uncertainty of estimates resulting from restricted sample size, are in parts reported for single-value-estimates (defaults). By this, conducting statistical uncertainty analysis using default values and confidence intervals is possible (see, e.g., Filipsson et al. 2011). Uncertainty due to sampling strategies (e.g., selection of study participants, response rates, regional differentiation) require a qualitative evaluation. Using the exposure factors (and variability indicators) published on a national level will result in general in an accepted state-of-the-art exposure assessment.

Uncertainties inherent in parameter values for exposure factors can be classified as sampling and non-sampling errors. Sampling errors arise from limited sample sizes in relation to the population size under consideration. The magnitude of this error is a function of (a) the variability of the measured attribute and (b) the sample size. In practice, we have to deal with the situation, that we have very low sample sizes, mostly for contamination measurement (esp. for food items, environmental measures). In these cases, the confidence intervals of the mean, the median and much more those for the upper quantiles show wide ranges. The selection of a type of distribution, in these situations, is based merely on scientific experience, not on data. If we only have data from selected subpopulations, we must assess the degree of representativeness for the target population and the expected effects of deviation. For selected scenarios and for statistical uncertainty calculation examples see e.g., Hammonds et al. (1994), IAEA (1989), RIVM (2009), U.S.EPA (2008, 2011).

More general problems might occur if exposure magnitude should be estimated for specific periods of the life span (child development, pregnancy, occupation). The age stratification of exposure factor handbooks is restricted. Especially for developmental studies, any changes in the exposure media, with respect to the sources and the pathways over the life stage should be considered. Each developmental stage requires the selection of specific scenarios, models, and appropriate age-related parameters – and a specific uncertainty evaluation (U.S. EPA 2006a).

Evaluating the Total Impact of Uncertainty

The objective of a full characterization of uncertainty of an exposure assessment includes transparency, the identification of key sources of uncertainty and an evaluation of the consequences of limited information in the decision making. A systematic qualitative characterization of the sources of uncertainty is encouraged, as it provides the appropriate degree of confidence in outcome and associated recommendations. Short overviews of concepts of and methods that might be useful for reading assessments and for the evaluation in parallel to preparing an exposure assessment are given in IPCS-WHO (2008), EFSA (2006), ECHA (2006), and BfR 2015.

A simple documentation scheme for identified uncertainties (Table 1) is proposed by IPCS-WHO (2008). The rows reflect the steps of exposure assessment, the column headers might be used as a guide for the identification of the mayor sources of uncertainty: Each element of the matrix contains many aspects that might contribute to the overall uncertainty of exposure assessment results. For each element a classification of the uncertainty should be assigned. IPCS-WHO (2008) recommends the terms (No, Medium, High or NA = "not applicable") for the quality and uncertainty assignments; EFSA (2006) proposed a ranking using two "+" and "−" signs indicating the direction and the magnitude of uncertainty for each subject of consideration. Short verbal descriptions of relevant uncertainty aspects for each cell of the table will support the transparency of the documentation.

Model Evaluation

The promise given by an exposure assessment is, that the estimated results would approximately reflect the real exposure situation for a defined population. According to the classification of exposure assessment methods, data and model-based exposure assessment belongs to the class of indirect measurement. They utilize existing

Table 1 Modified version of the EFSA (2006) and IPCS-WHO (2008) evaluation scheme

	Characteristics of uncertainty		
Sources of uncertainty	Overall level of uncertainty	Appraisal of the knowledge base	Subjectivity of choices
Scope/assessment objectives			
Scenarios			
Conceptual model			
Mathematical model			
Parameters			
Result(s)			

(secondary) data on chemical concentration, frequency, strength, and duration of contact, without doing any specific measurement of the outcome variable.

In contrast, a point-of-contact approach involves measurements of chemical concentrations at the point where exposure occurs to assess the outcome variable. These quantify concentration close to the interface between the person and the environment (e.g., by personal samplers, by personal protocols, or duplicates of dietary intake). If the time interval of contact is recorded, the average exposure per time unit might be calculated. This type of exposure estimate requires data from environmental samplers (e.g., measuring pollutants in indoor or outdoor), information of the individual's characteristics (e.g., breathing rates), time-budget in different environmental media like indoors, outdoors, in cars. An example from Payne-Sturges et al. (2004) shows, for instance, that personal sampler-based exposures measures show higher values than exposure calculations for indoor volatile organic compounds (VOC) exposure based on standard exposure factors. Personal monitoring might reflect the variance of exposure conditions better than exposure estimation.

Since the target variables of an exposure assessment should reflect the uptake of a substance in relation to the distribution volume (indicator: body weight), the most appropriate information for comparison exposure estimates stems from biomonitoring studies. For example, Xue et al. (2010) studied the intake of inorganic arsenic in the general US population with the objective to compare exposure model predictions with observed biomonitoring data (see also NHANES 2020). The goal was to quantify the distribution of total dietary arsenic exposure. Comparing model predictions with observed data, the evaluation was conducted via comparing exposure and dose-modeling predictions against duplicate diet data and biomarker measurements, respectively, for the same individuals. The distribution of the modeled exposure (biomonitoring with pharmacokinetic dose estimation) and the distribution of estimates of exposure matched well with the distribution of the Duplicate Diet estimates. Kurzius-Spencer et al. (2013) show that Total Diet Studies (TDS) might underestimate the dietary intake in comparison (a) to modeled dietary arsenic exposure based on 24-h duplicate diet samples intake, (b) exposure estimation using distributions as well as compared (c) to backward estimation of arsenic intake from 24-h urine measurement.

The use of biomarkers of exposure may provide a more detailed and less biased estimate of substance uptake and distribution than any indirect methods. But this requires full information about the distribution in the body and metabolism of the substance. The linkage of biomonitoring data to specific sources requires again exposure models (U.S. EPA 2006b). Burns et al. (2014) describe the sources of uncertainty associated with the results of most epidemiologic studies together with techniques that exist that can be applied to improve weight-of-evidence evaluations and risk characterization efforts. Only few evaluation studies have analyzed the predictive quality of exposure assessment for Human Biomonitoring data in detail. In consequence, the usage of exposure assessment should be directed to a comparison of prognostic results to regulatory recommendations for substance intake (like ADI, TDI, RfD, DNEL).

Sensitivity Analysis

Cullen and Frey (1999) define sensitivity analysis as the assessment of the impact of changes in input values on model outputs. Sensitivity analysis is used to determine how different values of an input, the independent variables, will impact a particular output, the dependent) variables, under a given set of assumptions. Sensitivity analysis studies the relationships between information flowing in and out of the model (Saltelli et al. 2004). Frey and Patil (2002) underline the use of sensitivity analysis in exposure assessment for an identification and comparison of sources of uncertainty that influence the target variables and the assessment conclusions. Furthermore, a sensitivity analysis is useful for providing insight regarding model verification and the robustness of models (Cullen and Frey 1999).

WHO/IPCS 6) Sensitivity analysis should be an integral component of the uncertainty analysis in order to identify key sources of variability, uncertainty or both and to aid in iterative refinement of the exposure model.

If risk managers like to consider the impacts of alternative regulatory or risk management choices than sensitivity analysis is inevitable. Any maximizing of benefits will depend on a comparison of results based on scenarios, models, and parameter alternatives. Incorporating variability and uncertainty into such comparative assessment is state-of-the art. Ignoring variability would mean neglecting existing differences in exposure conditions (e.g., over persons, over exposing situations, application/usage/contact of hazards). Ignoring uncertainty would mean providing results as reliable, even if they are questionable.

The identification of model variables which are not controllable by the risk management (e.g., breathing rates, body surface area, body weight) will inform about the limiting conditions that might not be changed by regulation, control or advice.

Uncertainty concerning causal analyses must be characterized qualitatively. A qualitative judgment of the overall uncertainty should be accompanied by a list of major sources of uncertainty and a quantification of the expected influence of variation of the parameters on the results. Variables that might not be modified can have a high impact on the outcome (e.g., breathing rates, water consumption). Using for instance physiologically based pharmacokinetic (PBPK) models to predict the dose of a chemical substance or metabolite will result in a strong dependency of many model parameters to organ weights or body weight (see, e.g., Farrar et al. 1989; Krewski et al. 1995; Clewell et al. 2000; U.S. EPA 2006b; Bois et al. 2010). The identification of all variables that have a high influence on the target variable requires quantitative analysis.

Building a ranked list that describes the influence of the input variables on the target variables requires statistical analysis. The goal is to quantify the degree of influence of the input variables variance on the variance of the target variable. An analysis of all possible outcomes for all ranges of the input variables (variability), together with a consideration of inherent quantitative (and numerical expressed

qualitative) uncertainties, is a scientific task that will call for an involvement of mathematical, statistical and exposure science expertise. This has to be considered if the models include many pathways and sources. If the global exposure model contains several submodels for influence factors, uncertainty evaluation should be conducted by scientists from different faculties.

Quantitative Sensitivity Analysis: Identification of Key Sources of Exposure, Uncertainty, and Variability

Since the efforts for a statistical sensitivity analysis should be balanced with respect to cost and time versus the expected gain of information, any uncertainty analysis should start with a screening step, which uses defaults for all parameters, evaluating the change of the outcome by stepwise changing these values. The identification of those input variables that have a strong influence on the variance of the target variables will indicate to variables with a high potential for possible exposure control (Frey et al. 2004).

The impact of variability might be controlled by a parameter-wise alternation of central tendency default to an upper-bound-estimate (e.g., the 95%- or 5%-quantiles). This procedure gives an overview about the 95% ranges of an influential variable, keeping all other influence variables on the mean or median (default for central tendency). In a similar manner, the impact of statistical uncertainty might be controlled by a parameter-wise alternation of the central tendency and/or the upper-bound-estimates using the confidence intervals (a fixed percentage) of these values, this describes the degree of uncertainty due to statistical reasons about the stability of estimates. These "One-At-A-Time" (OAT) methods (Murphy et al. 2004), changing always only one input parameter while keeping all other values constant, are strongly recommended at the screening level. A "tornado diagram," ranking the variables by the outcome change, might illustrate the relative importance of each input variable. This approach corresponds to the economic evaluation term "elasticity" that describes sensitivity as the ratio of the percentage change in one outcome variable to the percentage change in an input variable; it is in general calculated as the ratio of changes in natural logarithmic units: $E_{x,y} = \ln(\text{change in output y})/\ln(\text{change in input x})$ which corresponds approximately to (% output change in y)/(% input change in x). For an overview of graphical methods for presenting quantitative uncertainty, see, e.g., Ibrekk and Morgan (1987) and Edwards et al. (2012).

The main advantage of these One-At-A-time approaches is the fact, that the resulting changes in the model outcome are directly related to the change of input. These methods are simplified approaches for gaining information about the slope of change (mathematically the local partial derivate) at a given point in a multidimensional problem. An evaluation of results based on a One-At-A-Time approach is in general understandable for risk managers and the public. But it describes only the effects of variability or uncertainty for selected values, possible interactions between variables and nonlinearity are ignored. The behavior of the model might deviate if all variables show variation (and uncertainty) in a multivariate setting with dependencies and interaction (Cacuci 2003; Murphy et al. 2004).

Taking into account the combined effects of many input variables requires data sampling plans similar to experiments (e.g., Morris 1991) or simulation analysis. Looking at the variance impact is mostly done by Monte Carlo (MC) simulation. If the uncertainty of the parameters might only be described by ranges (numerical intervals), then these values might be used too (e.g., in a uniform distribution). If relevant association exists between the input variables, information about the correlation (covariance) structure should be used in the simulation model. Technically a Monte Carlo simulation (see, e.g., Fishman 1996) consists of random combinations of random variates following the distribution of each input variable. Repeating these random choices many times, the distribution of the exposure variable will represent the set of all possible combination of input variables, constraint by the distribution of input. Technically, these approaches are called probabilistic. If uncertainty is included into the simulation, the analysis changes from a one-dimensional variance propagation model into a two-dimensional analysis. WHO-tools that combine the output from the probabilistic hazard characterization with the probabilistic exposure to rapidly characterize risk and its uncertainty are described by Bokkers et al. (2017).

Using Monte Carlo simulations, the dependency of the output values on the input variability might be evaluated by a variance-based approaches. Typical methods are: (a) drawing scattergrams for visual inspection of dependency, (b) calculation of rank correlation calculation describing the ordinal degree of the "the more/less of input, the more/less of exposure). Ranking the correlation coefficients of the variables by the degree of association gives information that illustrates the positive and negative impact of the input variance and the degree uncertainty on the calculated exposure variance. (c) Calculation of a regression models with the input variables as independent and the exposure estimate as the dependent variable allows an integrative view. Using the standardized regression coefficients, allows a direct comparison (Cacuci 2003).

Introducing quantitative estimates of uncertainty into a variation-based model results in a calculation that consists of a (in general additive) mixture of variation and uncertainty. Uncertainty and variance compounds need to be represented by different variables within the model. They should be used as different terms in the (rank) correlation and regression calculations too. The combined effect might be evaluated. But this approach presumes a lot of information about the set of variables. In practice, a full sensitivity analysis including variability and uncertainty components is rarely done. If necessary due to model complexity or safety requirements, even more elaborated mathematical methods (e.g., Saltelli et al. 2004) might be appropriate.

If raw data sets from representative samples of the population (e.g., collected as national surveys) are available, then the original data set might be used as a calculation basis for exposure estimation. Using the individual consumption frequencies, the individual amounts eaten/used together with the individual anthropometric data (e.g., body weights), only the substance concentration distribution needs to be simulated according to the information about the type of distribution. The calculation results in a population-based estimate of exposure. This approach avoids the problems of data dependency, correlation, and interaction and reduces data and

model uncertainty. The techniques for a sensitivity analysis are the same as described above.

An approach of stratifying for homogeneous subgroups (e.g., age, sex, region, nutritional habits) will reduce the variability within each stratum (subgroup) but will keep the variation over the groups. Stratification rules should be guided by attributes that are reasonable linked to exposure. Differences in behavior (e.g., typical activities, consumption habits, product usage) might provide an indication for such a classification. This might be done by an exclusion of the exposure sources. Alternatively, the scope of the assessment might be changed, e.g., developing a model tailored for the "exposed fish-eater group" (see, e.g., EFSA 2012b).

If a sensitivity analysis identifies uncertainties in relation to knowledge about important data, this should be seen as a prioritizing argument for additional data collection or research. By this, it justifies a higher tier analysis and further iteration (Recommendation 2 of the IPCS-WHO 2008).

Interpretation of Uncertainty Characterization Results

Exposure assessment is based on scenarios, models, as wells as sufficient data about all influential exposure factors. The result of an exposure assessment is a prognosis about the expected level of exposure or the resulting body burden. Instead, direct methods of exposure assessment, such as personal sampling, duplicate studies, and human biomonitoring provide information on a measurement level. In consequence, exposure assessors and risk managers should balance the reasons for using prognostic techniques instead of direct exposure measurement methods. The main advantage of using exposure models over direct measurement is cost and time – in general at the price of a higher degree of uncertainty.

A prerequisite for exposure analysis is that the state of knowledge about all the different influence factors is sufficient and that existing knowledge might be translated into an exposure model. The assessor should keep in mind, why an assessment was required, which problems and which questions have trigged the request. Zehr (1999) pointed to the problem that "... unknowns, indeterminacy and ignorance, that exist in science are often transformed into uncertainty when reported to the public in order to make issues more manageable." A full and concise uncertainty assessment avoids this, it describes what is known and certain and what might be known doing additional research. Critical questions about the validity of the exposure assessment (accuracy, precision of prediction, validity, and objectivity) that should be expected in the course of risk communication can be anticipated and answered within an uncertainty analysis.

(IPCS/WHO 8) The uncertainty analysis should be subject to an evaluation process that may include peer review, model comparison, quality assurance or comparison with relevant data or independent observations.

The guiding principle eight of the IPCS-WHO document (2008) is related mainly to the questions if the exposure assessment is valid in the sense of scientific sound

quality and if it provides answers that are resistant to critical questions. Identification of uncertainty does not restrict the quality of the assessment. Although it might restrict the utility of an exposure assessment for regulatory or prevention-directed purposes, an uncertainty analysis increases the quality of information. A documentation of information about what is known, what is reasonable to expect, and what needs further clarification might have a high impact on the risk management process.

(IPCS/WHO 9) Where appropriate to an assessment objective, exposure assessments should be iteratively refined over time to incorporate new data, information and methods to better characterize uncertainty and variability.

Where the level of uncertainty is too high, only doing additional research, collecting more information, and/or obtaining better exposure measurements will change the situation.

Cross-References

- ▶ Assessment of Background Exposure and Additional Exposure by Human Biomonitoring
- ▶ Exposure Scenarios in Toxicology
- ▶ Human Biomonitoring: Its Importance in Toxicological Regulation
- ▶ Importance of Exposure Level for Toxicological Risk Assessment
- ▶ Limit Values and Guideline Values in Regulatory Toxicology

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