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Harmonization Project DRAFT Document for Public and Peer Review

DRAFT GUIDANCE DOCUMENT ON CHARACTERIZING AND COMMUNICATING UNCERTAINTY IN EXPOSURE ASSESSMENT

This project was conducted within the IPCS project on the Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals.

First draft prepared by the IPCS Working Group on Uncertainty in Exposure Assessment, under the Chairmanship of Dr Gerhard Heinemeyer. The contribution of Dr Alexandre Zenié, including editing and compiling the draft document, is gratefully acknowledged.

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FOREWORD

Harmonization Project Documents are a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO) and the United Nations Environment Programme (UNEP). Harmonization Project Documents join the Environmental Health Criteria (EHC) methodology (yellow cover) series of documents as authoritative documents on methods for the risk assessment of chemicals.

The main impetus for the current coordinated international, regional and national efforts on the assessment and management of hazardous chemicals arose from the United Nations Conference on Environment and Development (UNCED) held in 1992 and was reconfirmed at the 2002 World Summit on Sustainable Development. UNCED Agenda 21, Chapter 19, the “blueprint” for the environmentally sound management of toxic chemicals under the principles of sustainable development, has guided most international and national chemical-related activities. Chapter 19 is the agreed upon, endorsed international programme of action of governments for developing and implementing national programmes for management of chemicals within the principles of sustainable development.

The IPCS project on the Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals (Harmonization Project) is conducted under Agenda 21, Chapter 19. The Intergovernmental Forum on Chemical Safety (IFCS) Forum III, held in Salvador da Bahia in October 2000, agreed on Priorities for Action Beyond 2000, which further define the actions recommended to be taken. Forum III declared that by 2004, IPCS and the Inter-Organization Programme for the Sound Management of Chemicals (IOMC, which comprises seven intergovernmental organizations) should have ensured that recommendations for harmonized assessment approaches were available for terminology, cancer, and reproductive and developmental toxicology and that common principles for the assessment approach to other specific toxicological end-points, such as immunotoxicology, endocrine disruptors and ecotoxicology, should be adopted wherever possible.

The IPCS Harmonization Project, which is ongoing, states that “harmonization,” in the context of chemical risk assessment, should not simply be equated with standardization. It is not a goal of the project to standardize risk assessments globally, as that is considered to be neither appropriate nor feasible. Instead, harmonization is thought of as an effort to strive for consistency among approaches and to enhance understanding of the various approaches to chemical risk worldwide. Thus, harmonization is defined, in a step-wise fashion, as an understanding of the methods and practices used by various countries and organizations so as to develop confidence in, and acceptance of, assessments that use different approaches. It further involves a willingness to work towards convergence of these approaches or methods as a longer-term goal.

Achieving harmonization of approaches is considered to provide a framework for comparing information on risk assessment; understanding of the basis for exposure standards for specific chemicals in different countries; savings of time and expense by sharing information and avoiding duplication of work; and credible science through better communication among organizations and peer review of assessments and assessment procedures. The stated project mission is to ensure better chemical risk assessment and hence management practices that promote the protection of human health and the environment within the framework of sustainable development.

This ongoing project is overseen by a geographically representative Harmonization Project Steering Committee and a number of ad hoc Working Groups that manage the detailed work. Finalization of documents includes a rigorous process of international peer review and public comment.
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To be prepared for the final publication.
Guidance Document on Characterizing and Communicating Uncertainty of Exposure Assessment

Executive summary

This guidance has been developed as a basis for transparently characterizing uncertainties in exposure assessment to enable their full consideration in regulatory and policy decision-making process. These uncertainties are grouped under three categories, namely: parameter, model and scenario, with the guidance addressing both qualitative and quantitative descriptions. Guidance offered here is consistent with other projects addressing exposure in the WHO/IPCS harmonization initiative including a monograph on “IPCS Glossary of Key Exposure Assessment Terminology”, and a monograph on "Principles of Characterizing and Applying Human Exposure Models".

This document recommends a tiered approach to the evaluation of uncertainties in exposure assessment using both qualitative and quantitative methods, including both deterministic and probabilistic methodologies. It is intended for use by risk assessors who are not intimately familiar with uncertainty analysis. The key sections of the report include: definition and identification of different sources of uncertainties in exposure assessment, considerations for selecting the appropriate approach to uncertainty analysis as dictated by the specific objective, identifying the information needs of decision-makers, and recommendations for adopting a set of guiding principles for uncertainty analysis. The document also provides guidance on ways to consider or characterize exposure uncertainties during risk assessment and risk management decision-making, and on communicating the results. Illustrative examples based on environmental exposure and risk analysis case-studies are also provided.

The framework is considered applicable across a full range of chemical categories, e.g. industrial chemicals, pesticides, food additives and others. A tiered approach to choosing alternative methods for uncertainty analysis is proposed, with the degree of quantitative analysis increasing as progress is made through each tier. Finally, the monograph is developed to provide an insight into the complexities associated with characterizing uncertainties in exposure assessment and suggested strategies for incorporating them during human health risk assessments for environmental contaminants. This is presented in the context of comparability with uncertainties associated with hazard quantification in risk assessment.
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1 – Introduction

Individuals are exposed to wide variety of pollutants in various indoor and outdoor microenvironments through inhalation, dietary and non-dietary sources via ingestion or dermal contact during the course of a typical day. Exposure is defined as contact between an agent and a target, where contact takes place on an exposure surface over an exposure period (WHO, 2004; Zartarian et al., 1997). The agents of concern are usually chemicals, physical and biological agents; the targets are children, adults or sensitive subgroups in populations; the exposure surfaces are the external human boundaries (e.g., skin) or internal organs (e.g., gastrointestinal tract, lung surface); and the exposure duration may be short (i.e., from minutes to hours to a day) or long (i.e., from days to months or lifetime), depending on acute, intermittent or chronic toxicologic health considerations. The process of estimating or measuring the magnitude, frequency and duration of exposure to an agent, along with the number and characteristics of the population exposed, is called an exposure assessment. In some health studies the term “exposure assessment” may also include assessing the dose within the body after the agent enters into the body via ingestion, inhalation or dermal absorption. This absorbed dose of the agent or its metabolite is also known as the uptake.

Historically, risk assessments have included two principal components: one is hazard characterization, i.e. consideration of the inherent toxicologic effects of a chemical or an agent of concern, and the other is the assessment of the magnitude of likely human exposures and doses to an individual or a population resulting from contact with that chemical or that agent. Risk reduction is often achieved through exposure mitigation. Therefore, knowledge of the exposure is the basic prerequisite for risk characterisation and for characterizing subsequent risk management strategies. Public debate on risk assessments typically tends to focus on the hazardous properties of the substances of concern. However, risks cannot be reliably estimated if exposures and their uncertainties are not properly characterized and sufficiently quantified.

There are a number of aspects which must be taken into account in accurate estimation of exposure. Quantification of the magnitude and timing of personal exposures to chemicals or agents of concern requires the identification of sources and media of concern, key exposure microenvironments, and routes and pathways of exposure that contribute most to an individual’s exposure. Unfortunately, the data or information base on which to estimate emissions,
concentrations or exposures associated with each of these steps is sometimes
completely lacking, frequently incomplete, not representative or otherwise uncertain. Given that complete information is never available, exposure
assessors must make simplifying assumptions (e.g., use defaults), or rely on
data that are not necessarily representative of the populations or conditions of
interest (e.g., by extrapolating results which have been generated for other
purposes). For example, food consumption studies have been performed in
many countries to describe the eating habits of the population to improve
nutrition. Chemical food contamination, however, may be limited to very specific
food categories that are not considered in the more general consumption studies
and associated questionnaires. Extrapolations of such data may therefore lead
to uncertainties in the estimations resulting from reliance on such data.

Uncertainties in risk assessment include considerations related to missing,
incomplete and/or incorrect knowledge, as well as those associated with
ignorance and/or lack of awareness. Various levels of uncertainty should be
characterized as transparently as possible to ensure their adequate consideration
in decision making concerning the need for and nature of appropriate risk
management.

Uncertainty is distinct from data quality. Uncertainties are inherent, even when
exposure estimation is based on high quality data, e.g. its use in a wrong
scenario or model. On the other hand, assumed defaults in the absence of
specific data are generally conservative.

1.1 - Why uncertainty analysis?
An adequate characterization of the uncertainties in exposure assessment is
essential to the transparency of risk assessment and characterization of relevant
data gaps to improve defensibility; it is also a critical basis for informed decision-
making regarding the need for action to reduce risk and the nature of
appropriate measures. Uncertainties should be considered explicitly in each step
of the analysis and communicated throughout the process.

For exposure assessors, uncertainty analysis increases transparency and,
thereby, the credibility of the process. Consequently, worst case approaches can
be avoided and decision support improved. It also identifies important data
gaps, which can be filled to improve the accuracy of estimation.

The consideration and expression of uncertainty is given particular attention in
the Working Principles for Risk Analysis recently adopted by Codex: “Constraints,
uncertainties and assumptions having an impact on the risk assessment should
be explicitly considered at each step in the risk assessment and documented in a
transparent manner. Expression of uncertainty or variability in risk estimates
may be qualitative or quantitative, but should be quantified to the extent that is
scientifically achievable.” (bullet no. 23 of [Codex, 2005] p. 104).

“The report of the risk assessment should indicate any constraints, uncertainties,
assumptions and their impact on the risk assessment. Minority opinions should
also be recorded. The responsibility for resolving the impact of uncertainty on
the risk management decision lies with the risk manager, not the risk assessors.”
(bullet no. 25 of [Codex, 2005] p. 104).

1.2 – Consideration of uncertainty in the harmonization of risk
assessment methods
Guidance to increased transparency in communicating uncertainty in exposure
assessments contributes to the objectives of the International Programme on
Chemical Safety (IPCS) Harmonization Project by promoting consistency in the
presentation and defensibility of risk assessments. This includes increasing
common understanding of the nature of information limitations which impact on
the degree of confidence in the outcome of assessments and the resulting
appropriate impact on associated management measures and research
initiatives.

1.3 – Scope and objectives
The objective of this monograph is to provide an overview on the nature and
characterization of uncertainty in exposure assessments, including guidance on
the identification of sources of uncertainty, its expression and application not
only in risk assessment, but also risk management decisions, delineation of
critical data gaps and communication to decision makers and the public.

The content of this monograph is expected to be relevant to chemicals
regulators, the chemical industry and other stakeholders. It is intended to be
applicable across the full range of chemical applications, including industrial
chemicals, pesticides, food additives, industrial by-products and contaminants.

The framework included herein provides for both qualitative and quantitative
approaches to uncertainty analysis. It includes a tiered approach to methods for
uncertainty analysis, the degree of quantitative analysis increasing with the
complexity of assessment through each tier.

The monograph aims to also provide insight into the complexities associated with
exposure assessments. The document considers “uncertainty analysis” in an
inclusive manner and is not confined to statistical approaches alone.

Exposure analysts with varying levels of experience in uncertainty analysis are
the specific intended audience for the monograph. The guidance provided in this
monograph will enable exposure analysts to consider various aspects of
uncertainty throughout the whole assessment, particularly when undertaking
exposure assessments where uncertainty is identified as a significant problem.

However, since exposure assessment is an interdisciplinary activity, this
monograph is also expected to be a useful resource for a wider audience,
considering that each group may use the information contained herein for
different purposes. The monograph provides an overview of the types of
uncertainty encountered by an exposure analyst and provides guidance on how
uncertainty can be characterized, analysed and described in a risk assessment
and communicated effectively to a range of stakeholders.
The monograph will:

- Provide the historical context and background to uncertainty estimation in exposure assessment (chapter 1.4), including the distinction between uncertainty and variability (chapter 1.6);
- Establish “Guiding Principles” that are generally considered desirable goals or properties of an exposure assessment (chapter 7);
- Provide the rationale for characterizing uncertainty, including defining the exposure scenario and conceptual description (chapter 2);
- Identify sources of uncertainty (chapter 3);
- Identify the tiered approach (chapter 4);
- Describe qualitative and quantitative methods for characterizing uncertainty in exposure assessments (chapter 5);
- Discuss issues relevant to effective communication of the outcome of the uncertainty analysis (chapter 6).

1.4 – Historical context and background

The complexity of exposure assessments necessarily varies, depending upon their purpose. There has also been an evolution in approaches over time as methodologies have developed, increasing transparency and leading to the potential for greater convergence in methodology (i.e., harmonization).

Traditionally, single point estimates of (often) the maximum exposure of individuals were developed and compared with measures of dose response as a basis for risk characterization. Such estimates often lacked transparency in the context of the assumptions on which they were based and led to confusion in terminology (e.g., upper bounding, maximally exposed individual (MEI)).

In addition to precluding harmonization owing to insufficient transparency, important information relevant to risk management such as the population distribution of exposures was not provided and uncertainties (i.e., specification of the impact of critical data gaps and research priorities) were often not clearly articulated. As a result, transparency about the incorporated degree of conservatism was often insufficient. This may have resulted in less than optimum efficiency in allocation of resources to risk management versus data generation to better inform the characterization of risks.

More recently, there has been increasing emphasis on the characterization of the exposure of different individuals in the population. For example, the U.S. Environmental Protection Agency guidelines for exposure assessment issued in 1992 called for both a high end and central tendency estimates for the population (U.S. EPA, 1992). The high end was considered as that which could occur for the 90th percentile or higher of exposed individuals and the central tendency might represent an exposure somewhere near the median or mean of the distribution of exposed individuals.

Through the 1990s, there has been increasing emphasis also on characterization of the distinction between inter-individual variability and uncertainty in exposure
assessments (see (NRC, 1994) for example). During this time, there was also
growing interest and use of probabilistic simulation methods, such as those
based on Monte Carlo or closely related methods, as the basis for estimating
differences in exposures among individuals or, in some cases, in estimating the
uncertainty associated with any particular exposure estimate (U.S. EPA, 1997).

These converging developments have brought the field of probabilistic exposure
assessment from the background to a central part of exposure assessment today
in many applications. The transparency afforded by probabilistic characterization
and separation of uncertainty and variability in exposure assessment offers
potential benefits in the context of increasing common understanding as a basis
for greater convergence in methodology.

The historical content of uncertainty estimation in exposure assessment can be
traced to the convergence of developments in multiple disciplines. For example,
in 1946 Stanislaw Ulam and John von Neumann are typically credited with
creation of the “Monte Carlo” method for simulation of random events (see
(Metropolis and Ulam, 1949) and (Eckhard, 1987)). However, a paper by Lord
Kelvin in 1901 appears to apply concepts similar to Monte Carlo to a discussion
of the Boltzmann equation, and there are other precedents (Kelvin, 1901). The
modern incarnation of Monte Carlo was first used for prediction of neutron
release during nuclear fission, and has since been applied in a wide variety of
disciplines.

1.5 – Balancing uncertainties – Exposure and hazard
The extent of accommodation and characterization of uncertainty in a tiered
approach to exposure assessment must necessarily be balanced against similar
considerations with respect to hazard since the outcome of any risk assessment
is a function of comparison of the two. If, for example, there is limited
information to inform quantitatively of hazard and a result, a need to rely on
defaults, there is limited benefit to be gained in developing the exposure analysis
such that any increase in certainty is cancelled by uncertainties of greater
magnitude associated with quantification of critical hazard, as a basis for a
complete risk assessment.

Often, estimates of exposure are compared directly with benchmark doses or
concentrations (i.e., those that result in a critical effect of defined increase in
incidence such as 5 or 10%). Alternatively, they are compared either with a
Lowest-Observed-Effect-Level (LOEL), or No-Observed-Adverse-Effect-Level
(NOAEL), namely the highest concentration that does not lead to a toxic effect.
This results in a "Margin of Safety" (MOS) or - "Exposure" (MOE). Alternatively, estimates of exposure are compared with tolerable or reference
concentrations or doses, which are based on the division of benchmark doses
and/or concentration by no- or lowest-observed adverse effect levels by factors
which account for uncertainties in the available data.

Development of the tolerable or reference concentration or dose or consideration
of the adequacy of the margin of exposure or safety is generally based on
incorporation of a default uncertainty factor of 100 based on two 10 fold default
considerations or factors for each of interspecies differences and interindividual variability.

The NOAEL or benchmark dose/concentration is selected, then, generally to be at or below the threshold in animals; uncertainty factors are then applied to estimate the subthreshold in sensitive human populations, with a 10 fold default factor addressing interspecies differences (i.e., the variation in response between animals and a representative healthy human population) and another 10 fold factor accounting for interindividual variability in humans (the variation in response between a representative healthy human population and sensitive subgroups). While additional factors are sometimes applied to account for deficiencies of the database, the 100 fold default value is common.

Division of benchmark doses and/or effect levels by default uncertainty factors represents the lower end of a continuum of increasingly data-informed approaches to estimation of hazard. For example, where additional adequate quantitative data on interspecies differences or human variability in either toxicokinetics or toxicodynamics (mode of action) are available, chemical-specific adjustment factors (CSAFs) provide for their incorporation to replace appropriately weighted components of default uncertainty factors. This requires subdivision of default uncertainty factors for interspecies differences and interindividual variation into toxicokinetic and toxicodynamic components.

Physiologically based pharmacokinetic modelling sometimes constitutes a basis for replacement of default components of uncertainty for toxicokinetics and a portion of toxicodynamics. Where data are sufficient, a full biologically-based dose-response model addresses additional of the uncertainties for both interspecies differences and interindividual variability in both kinetics and dynamics.

As the extent of data and complexity of the analysis along this continuum increases, approaches are often presented probabilistically, including sensitivity analysis, with reference doses and/or concentrations of adequacy of margins of exposure being based on the proportion of the population to be protected. Increasingly, also, there is consideration being given to probabilistic presentation of default uncertainty factors as a basis for development of reference or tolerable concentrations and/or doses.

The extent of development and characterization of uncertainty associated with estimating exposure should take into account the nature of quantification of hazard in any risk assessment to ensure comparability of the two.

1.6 – Variability versus uncertainty
Exposure assessment informs decision making regarding protection of human health.

As Cullen and Frey (1999) point out, decision making regarding control of exposures is typically aimed at protecting a particular group, such as the entire population of a country, a highly-exposed subpopulation, random individuals
within a population, or specific individuals with a particular characteristic in common, e.g., children. As pointed out by NRC (1994), there is certainty that different individuals will have different exposures. For example, each individual may have a different behavioral (activity) pattern, dietary pattern, and physiological characteristics (e.g., breathing rates). For a given individual, these can change over time, and at any given time these vary between individuals. These differences lead to **variability** in the exposure levels of the individuals.

However, the true exposures are rarely known for a given individual, and are estimated using modeling procedures based upon available data. Uncertainty regarding exposure estimates arises due to limited availability of empirical information, as well as imperfections in the instruments, models or techniques used to develop representations of complex physical, chemical and biological processes. As described by NRC (1994), “uncertainty forces decision makers to judge how probable it is that risks will be overestimated or underestimated for every member of the exposed population”. Furthermore, because every individual can have a different exposure level, it is also possible that the estimate of uncertainty can differ among individuals.

Thus, the notions of intra-individual variability and uncertainty are distinct concepts, because they arise for different reasons. Variability is an inherent property of the system being modeled. In contrast, uncertainty can be conceptualized as dependent on the current state of knowledge regarding the system being modeled. From this perspective, uncertainty is more a property of the data than it is of the system being modeled. For example, the ability to make predictions regarding exposure will depend on the data and models available at the time that the prediction is made. Over time, perhaps “better” data might become available. Data could be considered better if it is more representative, more precise, or both. A model would be better than another if it had less systematic error and greater precision. As the quality of data and models improves, the amount of uncertainty inherent in a prediction decreases. Thus, uncertainty is reduced as the result of developing an improved knowledge base.

Two important considerations in probabilistic exposure assessment are whether to quantify uncertainty, and whether to separate it from variability within the analysis and output.

1. When **only variability** is quantified, the output is a single distribution representing a “best estimate” of variation in exposure. This can be used to estimate exposure for different percentiles of the population but provides no confidence intervals and may give a false impression of certainty.

2. When input distributions representing **variability and uncertainty are combined** (e.g., by “one dimensional” or 1D Monte Carlo), the output is again a single distribution, but now represents a mixture of variability and uncertainty (and is therefore wider, see Figure 1.1). It can be interpreted as an uncertainty distribution for the exposure of a **single member of the population selected at random**. This can be used to read off the probability of a randomly-chosen individual being exposed to any given level.
3. When variability and uncertainty are propagated separately (e.g., by “two-dimensional” or 2D Monte Carlo), they can be shown separately in the output. For example, the output can be presented as three cumulative curves: a central one representing the median estimate of the distribution for variation in exposure, and two outer ones representing lower and upper confidence bounds for the distribution (Figure 1.1). This can be used to read off exposure estimates for different percentiles of the population, together with confidence bounds showing the combined effect of those uncertainties that have been quantified.

Strategy or approach is then determined by the desired nature of the output: an estimate for a given percentile of the population with (option 3) or without (option 1) confidence bounds, or the probability of a randomly chosen individual falling below (or above) a given exposure (option 2).

Figure 1.1. Diagrammatic comparison between three alternative probabilistic approaches for the same exposure assessment. In option 1, only variability is quantified. In option 2, both variability and uncertainty are propagated together. In option 3, variability and uncertainty are propagated separately.

2 – Rationale of uncertainty

2.1 – Objective and concepts of exposure evaluation

Risk assessment is based on the three following steps (i) hazard identification, (ii) exposure assessment and (iii) risk characterisation. Uncertainty propagates through the process and may result from each step of the assessment and thus of the possible difference between the empirical (real) and the predicted (calculated) level of exposure. Insufficient knowledge about relevant exposure scenarios and corresponding model structure and its variables as well as three influence factors (Mosbach-Schulz, 1999) which are related to the input data, namely: diversity, variation and statistical uncertainty. Diversity is related to the real differences among groups of substances and individuals (e.g., age, sex). Variation describes existing differences within each group (e.g., behavioural, anthropometric). Statistical uncertainty encompasses that fraction of variability...
which is a result of given sample sizes (statistical errors of the estimates). Additional uncertainty with respect to samples might result from restrictions towards the degree of representativity and deviations in the degree from differential participation of subgroups, which might raise concern about systematic bias. Measurement error (especially in data from questionnaires), regional and temporal variance as well as aggregation bias (using average habits and consumption) might contribute to uncertainty.

The purpose of this section is to introduce the key questions which decision makers and stakeholders typically ask, which motivate the need for uncertainty analysis.

1. What is the variation and uncertainty of exposures among different members of an exposed population?
2. How precise are the exposure estimates?
3. How precise do exposure estimates need to be?
4. What are the key sources of uncertainty in the exposure assessment?
5. How should efforts be targeted to improve the precision of the exposure estimates?
6. How significant are differences between two alternatives?
7. How significant are apparent trends over time?
8. How effective are proposed control or management strategies?
9. Is there systematic error in the estimates?
10. What is the pedigree of the estimates (e.g., data, judgment, modeling)?

2.2 – Conceptual issues in uncertainty analysis
The ultimate goal of exposure assessment is to be able to link sources of e.g. pollutants to the agents concentration with which people come into contact, to exposure, uptake and dose in the target population group and to biological changes or effects which may lead to adverse health outcomes. Understanding these linkages and being able to measure and model the linkages and the impacts through exposure assessment is vital to scientific and public health policy evaluations. In conducting an exposure assessment, analysts are often challenged to address a number of technical questions, like:

1) Are the measurement data and/or the modeling estimates actually representative of the target group – either the general population or a selected sensitive sub-group?
2) How much measurement data is needed to represent the vulnerable population, such as children or the elderly?
3) How do we extrapolate from a relatively small sample to the larger group?
4) Does the exposure model capture the important exposure pathways / routes, and does it estimate the exposures properly?
5) Do the estimates also describe the variability and uncertainty associated with the exposure scenarios or processes, so that a realistic prediction of exposures and risks can be made?
Performing a qualitative or a quantitative variability and/or uncertainty analysis is often at the heart of addressing such important issues.

Exposure assessment, however, is a very complex process having different levels of uncertainties, with qualitative and quantitative consequences. Exposure assessors must consider many different types of sources of exposures, the physical, chemical and biological characteristics of substances which influence their fate and transport in the environment and their uptake, individual mobility and behaviours, different exposure routes and pathways, among others.

The objective of exposure analysis is to reflect real-world exposure scenarios and processes as far as possible. To transfer these concepts to exposure analysis, the situation in which the exposure takes place has to be described as closely as possible to the real-world exposure situation. Many steps have to be described, requiring different levels of information and respective uncertainties, which may be qualitative and/or quantitative. In an exposure model, all the steps needed to perform an analysis and its respective elements should therefore be examined during an uncertainty analysis. The aims of the uncertainty analysis in this context are to individually and jointly characterize and quantify the exposure prediction uncertainties resulting from each step of the analysis. In performing an uncertainty analysis, typically the main sources of uncertainties are first characterized qualitatively and then quantified using a tiered approach. In general, exposure uncertainty analyses attempt to differentiate between key sources of uncertainties: scenario uncertainties, model uncertainties and parameter uncertainties.

2.2.1 – The conceptual model

As pointed out in the WHO/IPCS monograph “Principles of Characterizing and Applying Human Exposure Models”, the first step of an exposure analysis need is to establish a “conceptual model” which characterises the framework designed to reflect the reality of human exposure and its processes. It defines the physical, chemical and behavioural information and exposure algorithms by which the model mimics a realistic exposure scenario. Accordingly, conceptual issues for uncertainty analysis must be considered.

An exposure assessment is based on the following three elements: “scenario”, “model” and “variable”. Uncertainties may arise from different use and understanding. The term “Model” is often used to describe exposure including all the circumstances, the scenarios and their mathematical expressions. The term “model” is also used for computer programmes to calculate exposure. In clinical pharmacology, a model characterises the mathematical expression of the uptake, distribution and elimination of a drug from the body. WHO defines “exposure model” as “a conceptual or mathematical representation of the exposure process”. This means that the model includes both concept and mathematical description of the exposure process.
**Figure 2.1. Conceptual model of formaldehyde exposure**

In Figure 2.1 a conceptual model of exposure to formaldehyde (molecular formula CH$_2$O) is given. It shows where formaldehyde comes from, sources of release and pathways of exposure, according to the above mentioned IPCS/WHO monograph.

Scenarios may be defined under the umbrella of this conceptual model. There are different levels of scenarios, such as that describing the release of CH$_2$O from furniture. Each of the exposures from one of the sources may be characterised by a particular scenario, but all of these scenarios may be combined to yield bigger and more complex scenarios, e.g. the inhalation exposure pathway. In this concept, the scenario describing the whole exposure including all sources and paths represents a very complex construction.

Why are scenarios important? First of all, a scenario is the basis for building a mathematical model (algorithm). According to the conceptual scenario, a model can be simple or complex. A model can describe the oral intake of juice having a certain CH$_2$O content, or it can describe the complex migration and release of CH$_2$O from a polyurethane foam and its further distribution into room air with subsequent inhalation exposure. The combination of all the above mentioned sources of CH$_2$O may also lead to complexity in the mathematical model.

**Conceptual issues in defining the steps of the assessment: What is a scenario?**  
WHO defines the term "exposure scenario" as follows: "A combination of facts, assumptions, and inferences that define a discrete situation where potential exposures may occur. These may include the source, the exposed population, the time frame of exposure, microenvironment(s), and activities. Scenarios are often created to aid exposure assessors in estimating exposure" (WHO, 2004).
3 – Sources of uncertainty

Uncertainties arise in various stages of exposure assessment. These uncertainties should be confronted as an integral part of the process rather than being limited to the final stage.

**Recommendation 1:**

*Uncertainty analysis should be an integral part of exposure assessment.*

The level of detail of the assessment may vary greatly, depending on the purpose for which it is carried out (*i.e.*, as a screening-level assessment or as a detailed, probabilistic assessment). The level of detail with which the uncertainty is analyzed will vary accordingly and should, as a rule, be consistent with the level of detail of the exposure assessment.

The objective of an uncertainty analysis is to determine differences in the output of the assessment due to the combined uncertainties in the inputs and to identify and to characterize key sources of uncertainty. To this end, a first step in the treatment of the uncertainty in an exposure study consists in the identification of the sources of uncertainty that are relevant for the study.

There are numerous methods for the subsequent qualitative and quantitative characterization of the relevant uncertainties. These methods are covered in sections 5.1 and 5.2 respectively.

This section gives an overview of different sources of uncertainty which may arise at different stages of the exposure assessment. Therefore, this chapter aims to systematically describe the steps of exposure assessment and the related sources of uncertainties.

Section 3.1 provides a brief overview of approaches and steps typically used in exposure assessment. Next, in section, 3.2 a taxonomy of the different sources of uncertainty is given. There are numerous texts providing schemes for the classification of sources of uncertainty. The classification given below follows in outline the one given in the U.S. EPA’s ‘Guidelines for Exposure Assessment’ (U.S. EPA, 1992).

**Recommendation 2:**

*The objective and level of detail of the uncertainty analysis should be based on a tiered approach and it should be consistent with the overall scope and purpose of the exposure and risk assessment. The amount of effort and detail should be consistent with the objective. All parts of the uncertainty characterization should be conducted in conformity with the specified objective and level of detail.*
3.1 - Approaches and steps in exposure assessment

Exposure assessment uses a wide array of techniques and information sources. The approaches to exposure assessment can be classified into four general categories:

- The use of professional (i.e., expert) judgment alone, with no attempt to use the direct or indirect approaches described below, to arrive at a qualitative assessment of the magnitude of exposure, i.e., “significant exposure is not expected from a small deviation of a specific value”.
- Use of direct approaches to quantify the exposure being assessed, using monitoring data from real life situations.
- Indirect approaches to quantify the exposure being assessed, using simulation and real-life modeling.
- Combined approaches to quantify the exposure being assessed, using partially direct and partially indirect approaches.

Common to all approaches are the following working steps:

- Specification of purpose and scope of the assessment.
- Building of the assessment scenario.

In addition, the quantitative approaches include:

- Description of the selected assessment approach, including monitoring and/or modeling steps, which specify the parameters needed in the assessment.
- Selection of data and specification of any assumptions.
- Execution of calculations.
- Documentation, interpretation and presentation of results.

3.2 – Nature of uncertainty sources

Uncertainty is the lack of knowledge of vital parts which are needed to perform an exposure assessment. Uncertainty can, at least in principle, be reduced by research or (additional) data collection.

Uncertainty pertains to different steps and approaches in the assessment. It can be classified into three broad categories:

- Scenario uncertainty: Uncertainty in specifying the exposure scenario which is consistent with the scope and purpose of the assessment.
- Model uncertainty: Uncertainty due to gaps in scientific knowledge which hamper an adequate capture of the correct causal relations between exposure factors.
- Parameter uncertainty: Uncertainty involved in the specification of numerical values (be it point values or distributions of values) for the factors which determine the exposure.
Classification using the three categories defined above is not as strict as it may seem, and the uncertainties may in practice arise in overlapping areas. For instance, numerical values of model parameters are often determined from the calibration of a model against some dataset. In this case, the parameter values may be uncertain both to the extent that this calibration dataset suffers uncertainty in measurement (parameter uncertainty) and that the model which is calibrated is not adequate for the situation (model uncertainty).

3.2.1 – Scenario uncertainty

A sound description of the scenario is an important prerequisite for modelling exposure or for interpreting measured exposure data. The description of the scenario governs the choice of the model and that of model variables (model parameters). The scenario description can be divided into several parts,

1. a description of the source of the chemical;
2. the characteristics of the release to the contacting environment, the distribution in and disappearance of the substance from that volume;
3. in any case of exposure analysis, the amount of a substance which will enter the body is calculated by the concentration of a substance in the contacting medium (i.e., in air, on skin or in media which can be eaten or swallowed) and an uptake rate (i.e., respiration rate, dermal absorption rate, consumption rate).

Also, behavioural data are important for characterising the exposure route, the frequencies and the duration of use/consumption.

Scenario uncertainty includes descriptive errors (e.g., wrong or incomplete information), aggregation errors (e.g., approximations for volume and time), errors of assessment (e.g., choice of the wrong model), and errors of incomplete analysis (e.g., overlooking an important exposure pathway).

Scenario uncertainty characterisation may firstly include a description of the information used for the scenario characterisation (scenario definition). This includes a description of the purpose of the exposure analysis. For regulation purposes, the level of the tiered approach is essential to describe the choice of data, whether defaults, upper bound estimates or other single point estimates, or distribution have been used. This choice may govern the kind of uncertainty analysis.

The definition of the scope and purpose of each exposure assessment provides the specifications for building the exposure scenario, which

• represents the real life situation that is to be assessed;
• provides the boundary limits of the assessment.

As pointed out before, the scenario uncertainty includes the “facts, assumptions and inferences” that are taken into consideration and used, but, in reality, are not actually representative of the scope and purpose of the assessment. These
sources of uncertainty typically include incomplete and/or non-relevant specification of the:

- Exposed population
- Agent(s) to be considered
- Spatial and temporal information
- Microenvironment (s)
- Population activity (ies)
- Source(s) of the agent(s) release
- Exposure pathway(s)
- Exposure event(s)
- Exposure route(s)

Incomplete and irrelevant specification of the above elements of the exposure scenario may be related to lack of knowledge, descriptive errors, aggregation errors, errors in professional judgment and incomplete analysis (U.S. EPA, 92).

The identification of the sources of the scenario uncertainty is a matter of interpretation of the scope and purpose of the assessment. It greatly depends on the clarity with which the scope and purpose are given by the frame for which the assessment is made. The sources of scenario uncertainty are directly related to additional uncertainty in the selection of the models and the parameters used in the assessment.

A clear decision whether the uncertainty is related to the scenario, model or data is sometimes difficult. There are, of course, overlaps and even expert opinions may deviate. The following short scenario descriptions represent examples which were primarily referred to scenario uncertainties.

Examples for scenario uncertainties:

1) lack of consideration of coffee as an important source for acrylamide exposure
2) lack of consideration of the dermal path in the assessment of exposure to insecticide sprays
3) lack of consideration of dust as an important carrier in the assessment of a non-volatile ingredient of a home-insecticide
4) characterisation of room air concentrations without consideration of air exchange

3.2.2 – Model uncertainty
In exposure assessments, mathematical and statistical models are often applied to represent the entire exposure process or parts of it. Models used in this sense quantitatively describe the relationship between its input parameters and the responses of the entire system (or part of it) to changes in these inputs.
certain extent a model is always a simplification of reality. The level of detail with which a model describes a system should be consistent with the objective of the assessment.

Model uncertainty is principally based upon (i) modeling errors i.e., non-consideration of parameters and (ii) relation (dependency) errors i.e. making wrong conclusions from correlations. The algorithm (mathematical formula) of a model should be selected in relation to the characterisation of the scenario. For example, if exposure to a slightly volatile substance takes place not only via inhalation, neglecting the e.g. house dust pathway in the model would lead to incorrect results. Another reason for model uncertainties may result from correlation errors among model parameters. For example, body weight correlates linearly or non-linearly with other physiological parameters, e.g. inhalation rate, body height, or body surface, or even with food intake. In many model estimations, those correlations have not been considered sufficiently.

In using models the following sources of uncertainty are to be considered:

1) Dependency errors
Lack of consideration of dependencies between parameters (be it by mistake or as a simplifying assumption) or incorrect inference of dependencies between parameters. For instance, anthropometric properties such as bodyweight, dermal surfaces and inhalation rate are correlated. Not including empirical proven correlation in a probabilistic assessment will yield incorrect exposure estimates.

Example:

1. Possible correlation between the frequency of use of a consumer product by a consumer and the amount used per use.
2. Expression of a linear relation by taking an exponential term
3. Dependency of body weight and breathing volume. The inhalation rate \(Q_{inh}\) depends on the basic metabolic rate (BMR) of humans by the equation:

\[ Q_{inh} = BMR \times H \times VQ \]

where

- \(H\) = oxygen uptake,
- \(VQ\) = ventilation equivalent.

On the other hand, the BMR depends on body weight (BW) as follows: \(BMR = BW \times CF + C\)

where \(CF\) is the correlation factor and \(C\) a numerical constant (Layton, 1993).

This leads to the relation of inhalation rate and body weight expressed as

\[ Q_{inh} = (BW \times CF + C) \times H \times VQ \]
2) Alternative model assumptions

It may be possible to build a model on different scientific assumptions for which the correct ones are unclear beforehand and can not be asserted e.g., the form of regression in regression models, the appropriate number and type of compartments and their connections in a compartmental model.

Example:

A number of skin absorption models have been described, all of them using physico-chemical properties of the substances (e.g., molecular weight, log $K_{OW}$ where $K$ is the octanol-water partition coefficient, as most important delimiters (Fiserova-Bergerova et al., 1990)). Usually the velocity of adsorption per area will be estimated. In simple exposure models, however, the absorption is simply expressed by a rate, i.e. an estimated absorbed percentage of the total amount of the substance.

3) Model detail

Simple model:

Simplifying assumptions in model development can be made for reasons of tractability and transparency, or due to a lack of knowledge of the correct model structure or system-parameters. For instance, the modeling of indoor air concentrations using well-mixed air conditions vs. including a description of diffusion of the chemical away from the source into the room air. Or, as another example, the aggregation of several compartments in a Physiologically Based Pharmacokinetic (PBPK) model into one compartment. Simplifications of a model may limit the extent of the model domain, or yield results with a higher degree of uncertainty, which may or may not be acceptable in view of the objective of the exposure assessment.

Example:

Simple worst case model for room air concentration, excluding e.g., air exchange rate

$$E = \frac{A}{V_{room}}$$

Complex model

Implementation of e.g. an emission model into this simple model would decrease the uncertainty of the scenario and the model. Also, the obtained result would be nearer to reality. However, making the model more complex may also
introduce new and additional uncertainties into the model, e.g. by taking low
good quality and thus high uncertain model variables. Making the model more
complex must therefore convincingly not implicate a decrease of the total model
uncertainty.

Example:

Estimation of the time-concentration curve by consideration of
increase (by emission) and decrease (air exchange) of the
concentration in a room.

\[
E(t) = E_0 e^{-\left(\frac{Q_{room}}{V_{room}}\right)t} + \frac{S + Q_{room} \times C_{ambient}}{Q_{room} + eV_{room}} \left[1 - e^{-\left(\frac{Q_{room}}{V_{room}}\right)t}\right]
\]

As illustrated, equation 1 represents the simplest algorithm to express a room
air concentration by dividing the amount by the room volume (EU TGD, 2003).
Equation 2 gives an example making the model for estimating the room
concentration more complex and time dependent. This example has been taken
from the source and ventilation scenario given in the ConsExpo tool (van Veen,
2001). Equation 1 is only used for worst case and low tier assessments.
Equation 2 is nearer to reality. If, however, the variables in the model are
uncertain, total uncertainty of the results revealed by this model may be
increased. These examples show that complexity of algorithms may introduce
different qualitative and quantitative uncertainties into an assessment.

4) Extrapolation
The use of a model outside the domain for which it was developed may introduce
an unknown level of uncertainty.

Example:

Using a model which was developed to estimate exposure to
pesticides when spraying plants indoors to describe an outdoor
situation will possibly not correctly capture the different
ventilation conditions outdoors.

5) Implementation of tools and software
Models implemented as software programs may suffer from errors in program
code, hardware errors as well as from differences in various computer operating
systems.

Example:

1. Running a model by using Windows XP with U.S.
   settings vs. Windows XP with German settings: A
   70,00 kg (or 70 kg) body weight value (written in a
very common European style) was read and calculated by one U.S. exposure model as 7000 kg, with similar errors in reading for other input parameters expressed with a decimal point!

2. Large Excel spreadsheets with hundreds of dependencies might contain errors.

### 3.2.3 - Parameter uncertainty

Exposure assessment involves the specification of values for parameters. Either for direct determination of the exposure or as input for mechanistic or empirical or distribution based models which are used to fill the exposure scenario with adequate information.

Numerical values for exposure parameters are obtained using various approaches (e.g., U.S. EPA Exposure Factors Handbook (U.S. EPA, 1997), EU Technical Guidance Document (EU TGD, 2003), German Xprob project (Mekel, 2003) and European KTL’s ExpoFacts (Vuori et al., 2006)).

#### 1) Measurement errors

Measurements of exposure parameters such as indoor air concentration levels of chemicals, time activity patterns, the chemical composition of consumer products, will as a rule be subject to errors inherent in the methodology used; errors in the analytical methods used to measure chemical concentration levels, inaccuracies in the survey data due to incorrect reporting by the participants. These errors may be categorised as random or systematic (biased) errors.

- Random measurement errors: these give rise to a variation around the 'true' value. For instance, reading a scale with certain accuracy, reporting the use of a consumer product by a consumer with an equal chance of under- or over reporting the actual use.

**Example:**

1) Emond et al. (1997) have shown that the method of sampling can significantly influence dust lead and children’s blood lead levels. They showed, by field measurements of lead-contaminated dust using five dust lead measurement methods, variation over methods and surface types. Technician effects, inadvertent field exposure to lead, contamination of collection equipment, and laboratory instrument error were found to contribute little to total measurement error.

2) The method chosen for studying nutrition habits may greatly influence estimations of exposure to food contaminants. The following approaches to protocol nutrition are possible:
(i) diet history protocol, where people are asked for their usual (e.g., over the last four weeks) nutrition,
(ii) the 24-h recall, where people are asked what they have eaten yesterday and
(iii) prospective diaries, where people protocol what they eat (Willett, 1998).

These diary studies may also include weighing of the food. The protocol period of these studies may vary from one day up to one week and may be repeated. All of these study designs have advantages and disadvantages, and their results have to be used according to the aim of the exposure assessment, e.g. whether a microbacterial outbreak or the chronic exposure to heavy metals shall be studied.

- Systematic bias of measurements. The average of the measurements of an exposure factor may differ from its ‘true’ value. This difference is termed the bias and may be a result of incorrect calibration of the measuring apparatus, of over- or understating in questionnaires.

Example:

1. Taking nutrition survey data from a diet history study to assess the uptake of microbials from an outbreak.

2) Sample uncertainty
When sampling data to estimate the distribution of an inherently variable quantity, the extent to which the sample is representative for the entire distribution will be a source of uncertainty. A small sample will not exhibit the same variation as is found in the entire population and may therefore not give the entire range of values found in reality. In addition, the sample may, for instance as a result of the selection criteria used to take the sample, be biased towards lower or higher values.

Example:

1. Data are not representative for the population, e.g. the sample was taken in a rural area, but the exposure of people living in a city was evaluated.

3) Surrogate data
In the absence of situation-specific data it is common that surrogate (or generic) data are used.
Example:

1. The technical Notes for Guidance on Human Exposure Assessment to Biocides (http://ecb.jrc.it/biocides/) provide indicative exposure values for a range of exposure scenarios (summarized in Annex 4 “Users guidance to Report 2002” (EU TNG, 2002)). These have been derived from experiments and are suggested to be used in similar situations. Uncertainty is associated with the data selection procedure, i.e. the degree in which the selected data are representative for the situation which it is supposed to describe.

4) Professional (expert) judgment

In situations where quantitative information on exposure factors is lacking, estimates of experts in the relevant field may be used. Uncertainty includes the choice of the expert selection procedure, the expert elicitation approach, review and validation.

Example:

1. Nine experts were asked to rank substances (1-5 rankings) in a list according to their toxicological relevance. All rankings were presented (Heinemeyer, personal communication, 2005).

5) Default data

Default values are reference values recommended for use for specific purposes, for instance in screening-level assessments. The level of uncertainty associated with the use of default values (which may be distributions) depends on the procedure and the quality of the background data set used to derive them.

Example:

1. Use of default parameters is one of the most frequently used approaches for exposure assessment where (i) data are lacking and for (ii) low tier estimations. Sometimes, worst case values are used as model defaults to consider the conservative approach of the assessment, in accordance with values at level 1 of uncertainty according to Paté-Cornell (1996).

These data can be characterised as model variables which are thought to represent a conservative value at or above the upper range. However, it is not representative of a
known range or distribution. Defaults are values which might not have been validated nor evaluated, they must not reflect representativity and do not meet other statistic criteria. Sometimes real data e.g. body weights are used as default. Of course, they are not defaults, because they are real point estimates.

Use of worst case parameters is implying a not known, but certainly high, degree of uncertainty into exposure assessments. Assessments that reveal risks by comparison of exposure and hazard data should be repeated taking approaches considering more realistic models and parameters.

6) Extrapolation uncertainty
Extrapolation is the inference of unknown data from known data, e.g., future data from past data, by analyzing trends and making assumptions. Uncertainty is introduced by questions as to how representative the extrapolated data is for the situation in which it is used.

Example:

1) The extrapolation of estimation made for adults to children would imply a high degree of uncertainty. Children are not little adults. Normally, exposures are referred to body weight, however, the mechanisms that govern the physiological mechanisms for absorption, distribution and elimination (including metabolism) of substances in the body are not linearly related to body weight but to body surface [BgVV, 2001]. Cohen Hubal et al. (2000) state that data about children's exposures and activities are insufficient and multimedia exposures to environmental contaminants cannot be assessed. In many assessments defaults are taken, due to a high degree of uncertainty in the assumptions and exposure estimates.

2) In the assessment of the uptake of a chemical after dermal exposure, for instance, the dermal permeability of the skin is often estimated using the Potts-Guy QSAR (Guy and Potts, 1992), which was derived from an experimental dataset of in-vitro measured steady-state skin permeations (Wilschut et al., 1995). Uncertainty in the use of a value for the skin permeation obtained this way comes from questions of how well a regression model based on $K_{ow}$ and molecular weight predicts the skin permeability of a chemical that was not in the original dataset, and how representative is the steady-state permeability measured in vitro for a (possibly) non-steady
state permeability in vivo.

3) A study designed for other purposes is used for exposure assessments, e.g. a food consumption survey performed for estimating “healthy nutrition” is used for exposure estimation of heavy metals.

7) Uncertainty in the determination of the statistical distribution used to represent distributed parameter values
When data sets are represented by probability distributions, uncertainty arises both in the choice of the appropriate distribution and the parametrization of this distributions. Data are often scarce in low probability areas, making a reliable fit to a distribution type problematic. Furthermore, the method of dealing with the possible presence of non-detects will have repercussions on the final distribution function.

Example of Choice of distribution for exposure estimation from iceberg salad consumption

As shown in the figure 3.1, the 95th percentile of cadmium intake from iceberg salad consumption revealed 17.88 µg/kg taking a lognormal distribution, 31.34 µg/kg taking a normal distribution and 194.52 µg/kg by simulation of a uniform distribution of the iceberg salad cadmium concentration. This example shows that the choice of distribution could make a large difference in the outcome of exposure assessment. Therefore the data should be fitted against several distribution functions to get the best fit parameters to decrease uncertainty. Data collection and data generation therefore play a predominant role in probabilistic approaches. The probabilistic methodology convinces the assessors to use transparent data and shows the need to use sound statistical and epidemiologic methodology to get representative data.
Figure 3.1. 95th percentiles of intake of cadmium (µg/day) from consumption of iceberg salad obtained by using five different distribution functions of the cadmium concentrations (Contamination data from the German "Lebensmittelmonitoring" programme see (BVL, 2006) and uptake data from the national nutrition survey 1988-1989 (Adolf et al., 1994)).

Recommendation 3:
Sources of uncertainty and variability should be systematically identified and evaluated in the exposure assessment.

4 – Tiered approach for uncertainty analysis
Typically, exposure and risk assessments conducted during regulatory evaluations are performed in a tiered or phased approach. A tiered approach refers to a process in which the exposure or risk assessments progress systematically from a relatively simple to more complex. An important feature of a tiered analysis is that the exposure or risk assessment and the accompanying uncertainty analysis may be refined in successive iterations.

4.1 – Regulatory background
Historically, much of the guidance for conducting environmental, exposure and risk assessments for air and multimedia pollutants has recommended considering a tiered or graded approach in regulatory impact and risk assessments. While the overarching consideration in conducting a tiered analysis is to increase the level of sophistication in the exposure, risk and uncertainty analysis when conducting a higher tier analysis, the exact form of analysis in a given tier may vary depending on the specific technical and regulatory context. For instance, US EPA’s Air Toxics Risk Assessment Technical Resource Manual (U.S. EPA, 2004) advocates a three tiered risk assessment process whereby each successive tier represents more complete characterization of variability and/or uncertainty as well as corresponding increase in complexity and resource requirements. In this scheme, Tier 1 is represented as a relatively simple screening-level analysis using conservative and/or default exposure assumptions. Tier 2 analysis is represented as an intermediate-level analysis using more realistic exposure assumptions and more sophisticated qualitative or quantitative uncertainty analysis approaches. Tier 3 is represented as an advanced analysis using probabilistic exposure analysis techniques, such as the one or two dimensional Monte-Carlo analysis methods, which incorporate full quantitative assessment of variability and uncertainty.

While Tier 1 analysis uses generic inputs, Tier 2 and Tier 3 analysis incorporate more site- or population-specific inputs in conducting the exposure and uncertainty analysis. A similar approach is also recommended by U.S. EPA in its Risk Assessment Guidance for Superfund (RAGS) Volume 3 Part A (U.S. EPA, 2001). In this guidance document, Tier 1 refers to conducting a point estimate risk assessment along with performing point estimate sensitivity analysis. In
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this document, Tier 2 analysis is characterized by conducting a one-dimensional Monte-Carlo analysis along with probabilistic sensitivity analysis. U.S. EPA (2001) assumes that a Tier 3 analysis involves the application of more advanced two-dimensional Monte-Carlo simulations, microenvironmental exposure modeling or Bayesian methodologies, for separately characterizing variability and uncertainty in the predicted exposure or risk results. On the other hand, California’s Office of Environmental Health Hazard Assessment (OEHHA) advocates a 4 tiered analysis under its “Hot Spots” air toxics program (OEHHA, 2000). In this state program in the U.S., Tier 1 analysis refers to a point estimate method, while Tier 2 refers to a point estimate method using site-specific exposure parameters. A Tier 3 approach is characterized as a stochastic approach using OEHHA developed or endorsed exposure parameter distributions. A Tier 4 approach is considered a stochastic approach using site-specific distributions for the model inputs and parameters where defensible (OEHHA, 2000). A tiered approach is also recommended for exposure assessment in the "implementation projects" for the new European chemicals legislation REACH (http://www.ecb.jrc.it/Documents/REACH/RIP_FINAL_REPORTS/RIP_3.2-1_CSA-CSRIEXPOSURE_SCENARIOS/RIP3.2-1_WP_1_ES_Final_28072005.doc).

4.2 – Determination of the tiered level

Determination of an appropriate level of sophistication required from a particular uncertainty analysis depends on the intended purpose and scope of a given assessment. Most often tiered assessments are explicitly incorporated within regulatory and environmental risk management decision strategies. The level of detail in the quantification of assessment uncertainties, however, should match to the degree of refinement in the underlying exposure or risk analysis. Where appropriate to an assessment objective, exposure assessments should be iteratively refined over time to incorporate new data, information, and methods in order to reduce uncertainty and improve the characterization of variability. Lowest-tier analyses are often performed in screening level regulatory and preliminary research applications. Intermediate-tier analyses are often considered during regulatory evaluations when screening-level analysis either indicates a level of potential concern or is not suited for the case at hand. The highest-tier analyses are often performed in response to regulatory compliance needs or for informing risk management decisions on suitable alternatives or trade-offs. Typically, higher-tier uncertainty analyses are based on more quantitative and comprehensive modeling of exposures or risks. The highest-tier analyses often provide a more quantitative evaluation of assessment uncertainties that also enable the regulators to determine how soon to act and whether to seek additional information on critical information or data gaps prior to reaching a decision.

The present monograph suggests a four tier approach for characterizing the variability and/or uncertainty in the estimated exposure or risk results.

4.3 – Tier 0 uncertainty analysis

Performed for routine screening assessments, where it is not feasible to conduct a separate uncertainty characterization for each case, default uncertainty factors which have been established for the type of problem under consideration may be
applied instead. These screening level assessments are designed to
demonstrate if the projected exposures or risks are unlikely to exceed reference
values. Currently, most regulatory applications require at the least,
standardized or default methodologies for conducting exposure and risk
assessments. These assessments also include often conservative defaults to
reflect assessment uncertainties. These screening-level assessments are
especially useful when it is not feasible to undertake more detailed sensitivity or
uncertainty analyses (e.g., for performing high-throughput screening
assessments). However, in conducting a Tier 0 uncertainty analysis it is
recommended that the default uncertainty factors should be derived from a more
substantial (higher-tier) uncertainty analysis, in consultation with risk
management, to ensure that the level of protection they afford is appropriate for
the class of problems they are intended for. Furthermore, it is suggested that
within this exercise, it may be done just once, but not repeated for every
individual assessment. Even though Tier 0 assessments are practical to conduct,
they are not suited for addressing problems which require a realistic
identification of key factors and exposure conditions contributing to assessment
outcomes and uncertainties. Higher tier assessments are often needed to
answer such questions.

Example:

1) A factor of 2 to 10 is often used as a default estimate of
upper bound uncertainties associated with ambient air
quality modeling of exposures to particulates or gaseous
pollutants outdoors.

2) The 1996 Food Quality Protection Act (FQPA) in the United
States advocated the use of a 10x safety factor to address
the special sensitivity of infants and young children to
pesticides when a screening level analysis of exposures is
performed using U.S. EPA’s Office of Pesticides’ SOPs
(Standard Operating Procedures).

4.4 – Tier 1 uncertainty analysis

Where the screening assessment indicates a concern, a more case-specific
uncertainty characterization is required to take account of any special
circumstances of the case in hand (e.g., anything that might justify a smaller
uncertainty factor than the default one) and to take account of any additional
(higher tier) data. Tier 1 analysis is intended to examine how likely it is, and by
how much, the exposure or risk levels of concern may be exceeded. Tier 1 is the
simplest form of this enhanced uncertainty analysis, mostly based on a
qualitative approach involving systematic identification and characterization of
different sources of assessment uncertainties. The main objective of Tier 1
uncertainty analysis is to characterize the influence of each individual source of
uncertainty independently on the results of the assessment. When the
uncertainty analysis is qualitative in nature, a description of the uncertainties in
each of the major elements of the exposure or risk analysis is usually described,
often presented together with a statement of the estimated magnitude and
direction of the uncertainty. Moreover, to the extent possible, the combined
effect of different sources of uncertainty on the exposure or risk predictions,
perhaps based on a weight-of-evidence methodology in the absence of
quantitative data, should also considered. This might in some cases provide a
sufficient basis to reach a risk management decision at Tier 1; if not, it would
form the basis for performing Tier 2 uncertainty analysis.

Example:

1. Examining the influence of the uncertainties in the key
   model variables (e.g., ranges of pollutant concentrations,
differences in exposure durations, inhalation rates, body
weights) which are used to predict the exposures of the
reasonably maximum exposed individuals.

2. Identifying the key sources of uncertainties in food
   consumption rates and dietary residue data during a
   dietary exposure and risk analysis, and subsequently
   examining their respective influence on model predictions.

3. Identifying and estimating the likely impact of key sources
   of uncertainties in conducting a residential pesticide
   exposure analysis (e.g., uncertainties associated with
   surface residue concentrations, frequency of hand contact
   with contaminated surfaces, pesticide transfer efficiency
   from different types of surfaces to the hand or body).

4.5 – Tier 2 uncertainty analysis
In a higher Tier analysis, semi-quantitative or quantitative sensitivity analysis,
interval or perhaps factorial and probability bound analyses are considered. The
semi-quantitative approach involves using available data to describe the
potential range of values for the assessment parameters, and performing
sensitivity analysis to identify the parameters with the most impact on the
exposure or risk predictions. Usually, Tier 2 uncertainty analysis consists of a
deterministic point estimate sensitivity analysis. Sensitivity analysis in this
context is often performed to identify the relative contribution of the uncertainty
in a given parameter value (e.g., inhalation rate, emission rate) or a model
component to the total uncertainty in the exposure or risk estimate. In a Tier 2
uncertainty analysis, the analysts usually examine the sensitivity of results to
input assumptions by using modified input values. A sensitivity analysis thus
performed may provide high, average or low predictions corresponding to the
range of values considered for each of the inputs. Typically, these calculations
are done for each variable at a time by holding the others constant, but can also
be done jointly by changing all of the inputs. The results of the sensitivity
analysis are typically presented as percent change in the baseline estimates
corresponding to incremental change in the inputs to the exposure model. In
some instances, when a single-value high-end and central tendency point
estimates do not provide sufficient information to the decision makers, a
qualitative uncertainty analyses can be conducted to determine the range of values within which the exposure or risk estimate is likely to fall and major factors that contribute to uncertainty (U.S. EPA, 2004). The sensitivity analysis conducted provides a range of exposure or risk estimates that result from combinations of minimum and maximum values for some of the parameters and mid-range for others (U.S. EPA, 2004). Typically, a quantitative uncertainty analysis is implemented through probabilistic modeling and statistical analysis methods under the most advanced Tier 3 uncertainty analyses. The decision to proceed to this next Tier depends mostly on the outcome of the Tier 2 analysis but also on the regulatory requirements or research significance of the particular assessment.

Example:

1) Deterministic sensitivity analysis performed during modeling of population exposures to ambient fine Particulate Matter (PM) by using high (H), medium (M), low (L) values during the analysis of the impact of uncertainties associated with key inputs and parameters on model predictions [e.g., time spent outdoors (H=95%, M=80%, L=50%), residential building infiltration fractions (H=0.7, M=0.5, L=0.2), deposition rates (H=0.4, M=0.3, L=0.10)].

2) Deterministic sensitivity analysis conducted using SOP algorithms for estimating children’s exposures to residential use pesticides, in which in addition to the SOP defaults, upper and lower-bound estimates are used for each of the exposure variables (e.g., for hand-to-mouth contact frequencies, amount of pesticides applied to surfaces, pesticide residue transfer coefficients) in the calculation of combined exposure uncertainties.

4.6 – Tier 3 uncertainty analysis
Tier 3 analyses rely upon probabilistic methods to characterize the individual and combined effect of input and parameter uncertainties on the predicted results. Moreover, in some Tier 3 analyses, separate contributions of variability and uncertainty to overall assessment uncertainties may be differentiated. The starting point for any Tier 3 analysis is the quantification of probability distributions for each of the key exposure or risk model input values (e.g., mean and standard deviation of fitted statistical distributions, such as normal or log normal distributions). These are often derived from existing measured or modeled values and in some cases based on expert judgments. Tier 3 uncertainty analysis examines the combined influence of the input uncertainties on the predictions by propagating either analytically (e.g., Taylor series approximation) or numerically (e.g., Monte-Carlo simulation) parameter and input value uncertainties, as appropriate. When few parameters are involved in the exposure calculations, analytic methods may be in order. However, more
complex model formulations often dictate the need for using numerical (e.g., Monte-Carlo, Bayesian) techniques for sensitivity and uncertainty analysis. Most Tier 3 uncertainty analyses do not differentiate variability from uncertainty (e.g., with one-dimensional Monte-Carlo analysis). Consequently, in such instances, it is not possible to readily distinguish the relative contribution of inherent variability in the exposure or risk factors from knowledge-based uncertainties to total assessment uncertainties.

More comprehensive quantitative analyses of exposure assessment uncertainties often rely upon modeling approaches which separately characterize variability and uncertainty in the model inputs and parameters. Examples include two-dimensional Monte-Carlo analysis, microenvironmental exposure modeling, geostatistical analysis of concentrations and exposure factors and Bayesian statistics. It is important to note that the interpretation of results from one-dimensional Monte-Carlo analysis can be different than those derived from two-dimensional Monte-Carlo analysis. For example, the distribution of values predicted by a one-dimensional Monte Carlo analysis (typically plotted as a cumulative distribution function) usually represents the uncertainty distribution for a randomly drawn individual from the study population; whereas the variability distribution generated from the first stage of a two-dimensional Monte-Carlo model represents the variability in the predicted median exposures. Methods used to characterize uncertainty in the inputs or parameters of the exposure models are based on either fitting parametric probability distributions or non-parametric probability distributions for the key variables selected for uncertainty characterization. Tier 3 probabilistic analyses also treat appropriately when moderate or strong correlations or dependencies exist between the model input variables. However, quite often not all the model variables are considered in a formal uncertainty analysis. For instance, human exposure model inputs which are based on survey data (e.g., time-activity data, dietary food consumption data) are often used in predicting only the inherent variability in exposures of individuals within the study population.

**Recommendation 4:**

The presence or absence of moderate to strong dependencies between inputs is to be discussed and appropriately accounted for in the analysis.
Figure 4.1. Relative Contribution by exposure route to predicted dose:
estimated population life-time average daily dose for arsenic for children
exposed to CCA-treated wood playsets and decks in warm climate regions
(Source: Zartarian et al., 2005)

In principal, the outputs from variability and uncertainty analysis are used to
quantify the nature of the variability in the predicted distribution of the
exposures and the uncertainties associated with different percentiles of the
predicted population exposure or risk estimates. The combined sensitivity and
uncertainty are also used in a two-dimensional probabilistic exposure or dose
assessment, in order to determine either the uncertainty about exposure (or
dose) at a given percentile or the uncertainty about percentile for given
exposure (or dose) level. In addition, uncertainty analysis based on multivariate
correlation and regression techniques shows the relative contribution of each
input to the overall analysis variance. These results are quite informative for
risk managers in identifying key factors influencing exposures and risks to
different segments of the population (e.g., the entire population or the
potentially highly exposed, such as those above the predicted 90th percentile
exposures). This type of detailed information is also valuable for targeting future
data collection activities on those information elements which have been
determined to contribute most to the overall uncertainty in the exposure or risk
results. Examples of output from a two-dimensional probabilistic exposure and
dose modeling application for a recent wood treatment case-study for children’s
potential exposure to arsenic, using EPA’s SHEDS model (Zartarian et al., 2005),
are shown in Figures 4.1 and 4.2.
Figure 4.2. Predicted uncertainty cumulative distribution functions associated with three selected variability percentiles of the estimated annual average daily dose distributions for arsenic exposures from contact with CCA-treated wood playsets and decks in warm-climate regions (Source: Zartarian et al., 2005)

Example:

1) Using a one-dimensional Monte-Carlo analysis to estimate population exposure and dose uncertainty distributions for Particulate Matter (PM), where model inputs and parameters (e.g., ambient concentrations, indoor PM emission rates form environmental tobacco smoked (ETS), indoor air exchange rates, building penetration values, particle deposition rates) are represented probabilistically with statistically fitted distributions to all available relevant data.

2) Conducting a two-dimensional Monte-Carlo modeling analysis for exposures to PM, air toxics, pesticides or metals, in which both variability and uncertainty in model inputs and parameters are separately quantified explicitly, and their individual as well as their combined effect on model results are estimated using either parametric or non-parametric sensitivity analysis techniques (Burke et al., 2001, Zartarian et al., 2005, Zartarian et al., 2006, Xue et al., 2006).

4.7 – Summary of the tiered approach

The amount of effort and detail devoted to analysing uncertainties should be proportionate to the needs of the problem, so a tiered approach is recommended.
Tier 0 exposure assessments which are commonly used for first tier screening purposes do not require an analysis of uncertainty on every occasion, provided they include appropriate conservative assumptions or safety factors to take account of uncertainty.

Higher-tier assessments do not require the quantification of every uncertainty. Therefore, a tiered approach is proposed where each individual application in an assessment may be treated at one of 3 tiers, beginning with qualitative approaches (Tier 1), and progressing to deterministic (Tier 2) or probabilistic approaches (Tier 3) when appropriate. Different applications may be treated at different tiers within a single assessment. Higher tier methods are targeted on the uncertainties which have most influence on the assessment outcome (Table 4.1). It is never practical to treat all uncertainties probabilistically so, even in a very refined assessment, some uncertainties will still be treated at the lower tiers.

<table>
<thead>
<tr>
<th>Uncertainty analysis</th>
<th>Tier 0 screening</th>
<th>Tier 1 qualitative</th>
<th>Tier 2 deterministic</th>
<th>Tier 3 probabilistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>application 1</td>
<td>standard conservative assumptions and/or uncertainty factors</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>application 2</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>application 3</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Table 4.1. Illustration of tiered approach to uncertainty analysis applied in three different applications. Tier 0 is a screening assessment in which all applications are assumed to be covered through the use of standard conservative assumptions and/or uncertainty factors. At Tier 1, all significant applications are considered at least qualitatively. To gain additional insights, sensitive input parameters may be treated both deterministically (tier 2) and probabilistically (Tier 3) as the application is progressing.

5 – Methods for uncertainty characterization

In any exposure assessment, there is some level of uncertainty attributable to the question formulation, source and pathway definition, scenario selection, data quality, and model reliability (accuracy and precision). In any exposure assessment, decision makers struggle with the questions of whether the assessment will lead them to make unwarranted choices and with what associated health, economic, and political consequences from their choices. To confront these questions, decision makers rely on exposure assessors not only to provide numbers but also to provide some measure of confidence about the reliability of these numbers. How the exposure question is formulated and set up using sources, pathway, and scenario definition can result in qualitative uncertainties that propagate through the later stages of an exposure analysis. The uncertainty of the input data is due to both the errors in measurements, the relevance of the data, and the impossibility of accounting for thevariability in time and space in the real system. Uncertainties in models derive from the input data as well as the sources of uncertainty which are inherent to the model structure, e.g. due to elementary processes which are not taken into account, to
the simplification of processes through mathematical equations, the limitation in spatial or temporal definition, etc. While there are protocols and software (i.e., Monte Carlo methods) which facilitate detailed quantitative assessment of parameter and model uncertainty, there are less explicit guidelines on how to confront and characterize the qualitative uncertainty deriving from question formulation, pathway definition, data selection, data relevance, etc. In this section both qualitative and quantitative approaches for characterizing uncertainty are described. We illustrate how these approaches apply and provide insight on the different tiers of an uncertainty analysis.

5.1 – Qualitative uncertainty characterization

5.1.1 – Rationale and objective
Currently, there are inconsistencies in the application and methodology for uncertainty analysis in exposure assessment. While several sophisticated quantitative techniques exist, their general application is hampered not only by their complexity (and resulting need for considerable supporting information) but also by the lack of methodology to facilitate the specification of uncertainty sources prior to the quantification of their specific weight.

In view of the often considerable limitations of available data supporting exposure assessment which sometimes limits the extent of uncertainty quantification and the need to explicitly identify sources of uncertainty prior to their quantification, this chapter provides an overview of existing concepts and proposes a harmonized approach for the qualitative analysis of uncertainty in exposure assessment.

The objective of qualitative characterization of uncertainty includes transparency in identifying key sources of uncertainty as an aid to risk managers who may need to make decisions in the absence of extensive datasets for substances with limited information; a prerequisite to quantification of uncertainty for substances with more extensive data.

The inclusive description of the components mentioned below is offered in the context of increasing transparency, although the limitations of available data may preclude consideration of all aspects. In all cases, the objective is to identify the principal sources of uncertainty which are influential in determining the outcome of the assessment and next steps, rather than simply listing unweighted gaps in information.

5.1.2 – Introduction
Depending on the purpose of an assessment (e.g., screening to designate non-priorities for further action) or the availability of relevant data, it is not always possible or necessary to conduct quantitative uncertainty analysis in exposure assessment, whereas systematic qualitative characterization of the sources of uncertainty is encouraged as it provides the appropriate degree of confidence in outcome and associated recommendations balanced by the identification of critical data gaps. It permits optimum use of (often) limited data in specific circumstances, with a clear delineation of relative uncertainty to indicate choices relevant to data generation and/or decision-making.
The methodology for qualitatively characterising the uncertainty of the exposure assessment consists of two basic steps:

1. specification of uncertainty sources
2. qualitative characterisation of uncertainty

Components of the second step are listed below. The extent to which each item is taken into consideration is a function of the nature of the relevant database and the purpose of the exposure assessment. The objective is to identify the sources of uncertainty which are most influential in determining the outcome of an exposure assessment:

1. qualitatively evaluate the level of uncertainty of each specified source
2. define the major sources of uncertainty
3. qualitatively evaluate the appraisal of the knowledge base of each major source
4. determine the controversial sources of uncertainty
5. qualitatively evaluate the subjectivity of choices of each controversial source
6. reiterate this methodology until the output satisfies stakeholders

![Figure 5.1](image)

**Figure 5.1.** Reduction of the number of sources of uncertainty through three qualitative evaluation steps: level of uncertainty, appraisal of the knowledge base and subjectivity of choices

The level of sophistication with which uncertainty is assessed is necessarily dependent on the use that will be made of the information [Paté-Cornell, 96]. Sometimes, a "level zero" analysis of uncertainty is all that is needed, simply asking: are there any major sources of uncertainty? At a slightly higher level,
we can ask: what are the controversial sources of uncertainty? If we believe that we can afford to incur this uncertainty, the analysis can end there.

The transparency of qualitative evaluation of uncertainty may be enhanced through the use of an evaluation matrix, where the considered sources of uncertainty are listed in lines and the characteristics of uncertainty (i.e., qualitative extent of the uncertainty) in columns together with their justification.

Included in a cell at the intersection of a source and characteristic is an evaluation of “not applicable”, “low”, “medium” or “high” according to the considered uncertainty characteristic for the source. The use of common descriptors in an evaluation matrix of this nature could lead to greater convergence in transparency by avoiding the use of inconsistent or uncritical terminology for uncertainty often included in exposure assessments.

<table>
<thead>
<tr>
<th>Qualitative evaluation of the uncertainty</th>
<th>Qualitative characterisation of uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Source of uncertainty</strong></td>
<td><strong>Characteristic of uncertainty</strong></td>
</tr>
<tr>
<td>source&lt;sub&gt;k&lt;/sub&gt;</td>
<td>&lt;value ∈ {NA, Low, Medium, High}&gt;</td>
</tr>
<tr>
<td>where NA stands for not applicable</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5.1. Qualitative evaluation matrix for exposure assessment**

Thus, each exposure assessment has one or more qualitative evaluation matrices depending on the selected characteristics of uncertainty.

The specification of the sources of uncertainty, the qualitative characterisation of uncertainty and the qualitative evaluation of the uncertainty are analysed below.

5.1.3 - Specification of the sources of uncertainty

The three main classes of sources of uncertainty (chapter 3.2) are ‘scenario uncertainty’, ‘model uncertainty’ (both in conceptual model formulation and mathematical model formulation) and ‘parameter uncertainty’ (both epistemic and aleatory). The nature and extent of the qualitative characterization of these sources of uncertainty is necessarily dependent on the objective of the exposure assessment and the appropriate form of output for its intended purpose. Prior to initiating the development of any assessment, its intended purpose must be clearly articulated.

<table>
<thead>
<tr>
<th>Procedure for specifying sources of uncertainty</th>
<th>Approaches and considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Source</strong></td>
<td><strong>Approaches and considerations</strong></td>
</tr>
<tr>
<td>Scenario</td>
<td>Specifying the:</td>
</tr>
<tr>
<td>1) agent(s) to be considered and the source(s) of the released agent(s)</td>
<td></td>
</tr>
<tr>
<td>2) exposed population</td>
<td></td>
</tr>
<tr>
<td>3) microenvironment</td>
<td></td>
</tr>
<tr>
<td>4) spatial and temporal information (e.g., geographic applicability and seasonal applicability)</td>
<td></td>
</tr>
<tr>
<td>5) risk management measures</td>
<td></td>
</tr>
<tr>
<td>6) population activity(ies)</td>
<td></td>
</tr>
<tr>
<td>7) exposure pathway(s)</td>
<td></td>
</tr>
<tr>
<td>8) exposure event(s)</td>
<td></td>
</tr>
<tr>
<td>9) exposure route(s)</td>
<td></td>
</tr>
</tbody>
</table>
Models

- Specifying the:
  1) linking the selected conceptual model to the adopted scenario
  2) model assumption(s)
  3) model dependency(ies)
  4) model structure related to (a) resolved processes and (b) unresolved processes
  5) model equation(s)
  6) model implementation and technical model aspects (e.g., errors in software and hardware)

Parameters

- Specifying the:
  1) data source(s)
  2) data dependency(ies)
  3) data type (e.g., measurement data, modelling data, default data, expert judgement)
  4) data value(s) including the method(s) generating the data
  5) data unit

Table 5.2. The approaches and considerations for specifying each source of uncertainty

The uncertainty of the ‘conceptual model’ source concentrates on the relationship between the selected model and the scenario under consideration.

Each of the following basic sources of uncertainty, ‘scenario’, ‘model’ and ‘parameter’, can be further detailed in order to characterise each basic component separately:

<table>
<thead>
<tr>
<th>scenario</th>
<th>agent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>exposed population</td>
</tr>
<tr>
<td></td>
<td>microenvironment</td>
</tr>
<tr>
<td></td>
<td>spatial and temporal information</td>
</tr>
<tr>
<td></td>
<td>population activity(ies)</td>
</tr>
<tr>
<td></td>
<td>risk management measures</td>
</tr>
<tr>
<td></td>
<td>exposure pathway(s)</td>
</tr>
<tr>
<td></td>
<td>exposure event(s)</td>
</tr>
<tr>
<td></td>
<td>exposure route(s)</td>
</tr>
<tr>
<td>model</td>
<td>model assumption(s)</td>
</tr>
<tr>
<td></td>
<td>model dependency(ies)</td>
</tr>
<tr>
<td></td>
<td>model structure</td>
</tr>
<tr>
<td></td>
<td>equation(s)</td>
</tr>
<tr>
<td></td>
<td>model implementation</td>
</tr>
<tr>
<td>parameter</td>
<td>data source(s)</td>
</tr>
<tr>
<td></td>
<td>data dependency(ies)</td>
</tr>
<tr>
<td></td>
<td>data value(s)</td>
</tr>
<tr>
<td></td>
<td>data unit</td>
</tr>
</tbody>
</table>

Table 5.3. Detailed sources of uncertainty

Recommendation 5:

Data, expert judgment, or both should be used to inform the specification of uncertainties for scenarios, models, and inputs.
5.1.4 - Qualitative characterisation of uncertainty

The aim of qualitative characterisation of uncertainty is to provide a conceptual basis for the systematic assessment of uncertainty in decision support processes, such as exposure assessment. It focuses on uncertainty perceived from the point of view of assessors providing information to support policy decisions, i.e., uncertainty regarding the analytical outcomes and conclusions of the exposure assessment.

**Figure 5.2.** The three-dimensional characteristics of uncertainty (adapted from [Walker et al., 03])

5.1.4.1 - Level of uncertainty

The ‘level of uncertainty’ is essentially an expression of the degree of severity of the uncertainty, seen from the assessors’ perspective.

A scale ranging from ‘Low’ to ‘High’ can be used to assess the sensitivity of the exposure assessment outputs to changes in the other sources being specified, as illustrated in Figure 5.3.

**Figure 5.3.** The scale of level of uncertainty (adapted from [Walker et al., 03] and [Krayer von Krauss and Janssen, 05])
A ‘Low’ level on the scale implies that a large change in the source would only have a small effect on the results, a ‘Medium’ level implies that a change would have a proportional effect and a ‘High’ level implies that a small change would have a large effect.

The most obvious example of a low level of uncertainty is the measurement uncertainty associated with parameters. Measurement uncertainty stems from the fact that measurement can practically never precisely represent the ‘true’ value of that which is being measured. Uncertainty due to ignorance can be further divided into reducible ignorance and irreducible ignorance. Reducible ignorance may be resolved by conducting further research, which implies that it might be possible to achieve a better understanding. Irreducible ignorance applies when neither research nor development can provide sufficient knowledge about the essential relationships. Irreducible ignorance is also called indeterminacy [Walker et al., 03].

5.1.4.2 - Appraisal of the knowledge base

‘Appraisal of the knowledge base’ focuses on the adequacy of the available knowledge base for the exposure assessment (e.g., identification of data gaps and their impact on outcome). It involves questions like: What quality criteria are relevant for answering the assessment questions? What knowledge and methods are needed to obtain answers of the required quality? In the light of existing controversies and weaknesses in the knowledge base, what are the most significant bottlenecks? What effect do these bottlenecks have on the quality of the results and which actions should be taken to clear them?

Examples of criteria for evaluating the uncertainty of the knowledge base are accuracy, reliability, plausibility, scientific consistency and robustness. These criteria are detailed in Table 5.4.

<table>
<thead>
<tr>
<th>Appraisal of the knowledge base</th>
<th>Approaches and considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criteria</strong></td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>1) establishing the knowledge base needed to obtain answers of the required quality</td>
</tr>
<tr>
<td></td>
<td>2) signalling controversies with respect to the knowledge base</td>
</tr>
<tr>
<td></td>
<td>3) identifying the most important bottlenecks in the available knowledge</td>
</tr>
<tr>
<td></td>
<td>4) determining the impact of these bottlenecks on the quality of the results</td>
</tr>
<tr>
<td></td>
<td>5) assessing the assumptions covering the knowledge gaps</td>
</tr>
<tr>
<td>Reliability</td>
<td>1) criticizing the knowledge base severely on factual and methodological grounds</td>
</tr>
<tr>
<td></td>
<td>2) identifying the scientific status of the knowledge base</td>
</tr>
<tr>
<td></td>
<td>3) determining the quality soundness of the knowledge base</td>
</tr>
<tr>
<td></td>
<td>4) assessing the appropriateness of judgmental estimates of level of confidence</td>
</tr>
<tr>
<td>Plausibility</td>
<td>1) determining the completeness of the knowledge base</td>
</tr>
<tr>
<td></td>
<td>2) acknowledging ignorance when applicable</td>
</tr>
<tr>
<td></td>
<td>3) analysing the possibility of changes in underlying processes over time</td>
</tr>
<tr>
<td></td>
<td>4) considering well established observations</td>
</tr>
<tr>
<td>Scientific Consistency</td>
<td>1) assessing the consistency of scientific support</td>
</tr>
<tr>
<td></td>
<td>2) assessing the maturity of the underlying science</td>
</tr>
<tr>
<td></td>
<td>3) assessing the scientific limitations</td>
</tr>
<tr>
<td></td>
<td>4) analysing the degree to which understanding is based on fundamental concepts tested in other areas</td>
</tr>
<tr>
<td>Robustness</td>
<td>1) assessing the predictability of the values and of the results</td>
</tr>
<tr>
<td></td>
<td>2) assessing the dependency relationships</td>
</tr>
</tbody>
</table>
A scale ranging from ‘Low’ to ‘High’ can be used to evaluate the uncertainty of the knowledge base, as illustrated in Figure 5.4.

**Figure 5.4.** The scale of knowledge base uncertainty (adapted from [van der Sluijs et al., 05])

### 5.1.4.3 - Subjectivity of choices

‘Subjectivity of choices’ delivers insight into the choice processes of the exposure assessors when they have made assumptions during the exposure assessment, and particularly focuses on value-ladenness of assumptions, starting from the viewpoint of the exposure assessors carrying out the assessment.

Examples of criteria for evaluating the subjectivity of choices are: choice space, inter-subjectivity among peers and among stakeholders, influence of situational limitations (e.g., money, tools and time) on choices, sensitivity of choices to the analysts’ interests and influence of choices on results. These criteria are detailed in Table 5.5.

<table>
<thead>
<tr>
<th>Subjectivity of choices</th>
<th>Criteria</th>
<th>Approaches and considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>choice space</td>
<td>1) spanning alternative choices</td>
</tr>
<tr>
<td></td>
<td>intersubjectivity among peers and among stakeholders</td>
<td>1) specifying the similarity of choices among peers and among stakeholders</td>
</tr>
<tr>
<td></td>
<td>influence of situational limitations (e.g., money, tools and time) on choices</td>
<td>2) specifying the controversy of choices among peers and among stakeholders</td>
</tr>
<tr>
<td></td>
<td>sensitivity of choices to the analysts’ interests</td>
<td>1) determining the influence of situational limitations on the choices</td>
</tr>
<tr>
<td></td>
<td>influence of choices on results</td>
<td>1. assessing the sensitivity of the choices to the analysts’ interests</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1) determining the influence of the choices on the results</td>
</tr>
</tbody>
</table>
Table 5.5. detailed specification of each criterion evaluating the uncertainty related to the subjectivity of choices

A scale ranging from ‘Low’ to ‘High’ can be used to evaluate the uncertainty of the subjectivity of choices, as illustrated in Figure 5.5.

Figure 5.5. The scale of uncertainty related to subjectivity of choices (adapted from [van der Sluijs et al., 05])

5.1.4.4 - Qualitative evaluation of the uncertainty
Each identified source of uncertainty is evaluated against the selected characteristic of uncertainty (i.e., not applicable or low, medium or high) which leads to a map of qualitative values.

In a first step, both exposure assessors and risk managers should give a qualitative indication of the level of uncertainty of each source and the way this uncertainty could influence the final output of the exposure assessment.
In a second step, both exposure assessors and risk managers should look closely at the appraisal of knowledge base to see where the reasons for the recognised levels of uncertainty are and what actions (such as research) can be discriminated to deal effectively with that uncertainty in order to make the assessment more robust.
In a final step, both exposure assessors and risk managers and eventually the involved stakeholders should understand the range of factors influencing the subjectivity of choices and assumptions of exposure assessors.

It is essential to provide risk managers with an assessment of the overall degree of uncertainty in the assessment outcome. This should integrate all three dimensions of uncertainty, from all parts of the assessment. Integration of qualitative uncertainties is inevitably subjective, so it is important to document the reasoning so that others can evaluate the conclusions that are reached. This
can be done by tabulating the main uncertainties identified in the assessment, as illustrated in Table 5.6, and by providing a brief explanation of the weights given to them in reaching an overall conclusion. In addition, a textual description of the qualitative characterization of tabular output below should include an indication of overall uncertainty, based on the collective impact of each of the sources. Table 12.2 in chapter 12 details the evaluation throughout the three-dimensional characteristics. There should also be an overall conclusion on sensitivity – i.e., those aspects which have the most significant impact on the outcome of the assessment; as better data collected on these features would considerably reduce the measure of uncertainty. An example of the overall conclusion is given in the case study of chapter 12 (section 12.5).

<table>
<thead>
<tr>
<th>Sources of uncertainty</th>
<th>Characteristics of uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Level of Uncertainty</td>
</tr>
<tr>
<td>Scenario</td>
<td>High</td>
</tr>
<tr>
<td>Model</td>
<td>Conceptual</td>
</tr>
<tr>
<td></td>
<td>Mathematical</td>
</tr>
<tr>
<td>Parameters</td>
<td>High</td>
</tr>
</tbody>
</table>

Table 5.6. Example of tabular approach to summarising the main uncertainties affecting an assessment (see Table 12.3 in chapter 12)

5.1.5 - Conclusion

Through the review of approaches to explicit qualitative consideration of contributing sources, this chapter offers a framework to facilitate and promote a qualitative consideration of the impact of uncertainties on exposure assessment where data are very limited and/or as a prelude to more quantitative characterization of uncertainties. Transparency to address uncertainties and specification of those which impact most on outcome is essential to effective decision-making in risk management.

5.2 – Quantitative uncertainty characterization

This section provides an overview of common methods for quantitative uncertainty analysis. Furthermore, consideration is given to methods for analysis of both variability and uncertainty. In practice, commonly used methods for quantification of variability, uncertainty, or both are typically based on numerical simulation methods such as Monte Carlo simulation or Latin Hypercube sampling. However, there are other techniques that can be applied to the analysis of uncertainty, some of which are non-probabilistic. Examples of these are interval analysis and fuzzy methods. The latter are briefly reviewed. Since probabilistic methods are commonly used in practice, these methods receive more detailed treatment here. The use of quantitative methods for variability and uncertainty is consistent with, or informed by, the key hallmarks of data quality, such as appropriateness, transparency, accuracy, and integrity, as described in the IPCS Draft Document on Data Quality Issues in Exposure Assessment (WHO, 2006).
5.2.1 – Intervals and probability bounds

Ferson (1996) points out that there is a class of problems in which information may be known regarding upper and lower bounds for a particular variable, but not regarding a probability distribution. The model output in such cases is an interval, rather than a distribution. Such problems are more appropriately dealt with using interval methods rather than imposing probabilistic assumptions upon each input. Interval methods can be extended to situations in which marginal probability distributions are specified for each model input but for which the dependence between the distributions is not known. Thus, rather than assume statistical independence, or any particular correlation or more complex form of dependency, a bounding technique can be used to specify the range within the model output distribution must be bounded.

Some would argue that if there is sufficient information upon which to quantify ranges, then there is also likely information upon which to base a judgment regarding the type of distribution that could be used to describe uncertainty in the input. Interval methods, however, may be useful for problems in which there may be complex dependencies between inputs but for which the dependencies are not known. A disadvantage of interval methods is that the predicted intervals for a model output can be quite wide, since they are informed only by the endpoints of the ranges for each input. Interval methods can be useful as a quality assurance check on the results of a Monte Carlo simulation or other method, since the results from other methods should be enclosed by the results from the interval method.

As a simple illustration of interval methods, consider the example given by Ferson (1996) pertaining to multiplication of two inputs. Input $A$ has an interval of $[0.2, 0.4]$ and Input $B$ has an interval of $[0.3, 0.5]$. The interval for the model output is $[0.06, 0.2]$. The output interval is the narrowest possible interval that accounts for all possible forms of dependence between $A$ and $B$.

Many analysts are tempted to assign a uniform distribution when only a minimum and maximum value is specified for an input. Such an assignment is justified on the theoretical basis of maximum entropy. However, it is clear that assuming a probability distribution within the specified range involves presuming more information than simply assigning an interval. Furthermore, if inputs $A$ and $B$ are each assigned distributions, then there is the question of whether the two inputs are statistically independent. Each of these assumptions implies more information on the part of experts or the analyst. Ferson (1996) argues that if such information is not available, then there is not justification for making such assumptions simply because they are convenient. Of course, in many cases, the state of knowledge may adequately support judgments regarding the probability distribution for each input and the nature of the dependence, if any, between them.

A variation on the use of intervals is the use of discretized strata to represent a continuous distribution. For example, as described in Section 11.2.4, the “factorial design” method involves representing inputs to a model as nominal values that are described as low, medium, and high. The numerical estimates
associated with these ranges could be the minimum, median, and maximum values from the corresponding continuous distribution. A similar but more formal method, known as Discrete Probability Distribution (DPD) arithmetic, involves representing a continuous distribution as a discrete distribution, also with low, medium, and high ranges. However, the numerical values of a DPD for each of these three ranges should be the mean of each range, in order to more accurately approximate the mean and central moments of the original continuous distribution.

5.2.2 – Fuzzy methods
Fuzzy methods were introduced to represent and manipulate data and information possessing no statistical uncertainties (Zadeh, 1965). Fuzzy methods differ from statistical methods in that they do not conform to axioms of probability. Fuzzy methods are based upon fuzzy sets (e.g., Jablonowski, 1998). An element of a fuzzy set, such as a particular number for an input to a model, has a grade of membership in the set. The grade of membership is different in concept from probability and is often referred to simply as “membership.” Membership is a quantitative noncommittal measure of imperfect knowledge. For example, suppose that the height of a person is classified as “tall” or “not tall.” In a fuzzy representation, the person’s height might be given a partial membership of, say, 0.7 in the tall set, and therefore would have a partial membership of 0.3 in the “not tall” set.

Fuzzy methods are suitable for approximate reasoning (U.S. EPA, 2001), especially for analysis of systems where uncertainty arises due to vagueness or “fuzziness” or incomplete information rather than due to randomness alone (Evans et al., 1986). The advantage of these methods lies in that they can characterize non-random uncertainties arising from vagueness or incomplete information and give an approximate estimate of the uncertainties. The limitations of the fuzzy methods are: (1) they cannot provide a precise estimate of uncertainty, but only an approximate estimation; (2) they might not work for situations involving uncertainty arising from random sampling error.

5.2.3 – Probabilistic methods
Probabilistic methods for quantification of variability and uncertainty are used in practice to estimate the exposures for different percentiles of exposed populations and to estimate the precision of the exposure estimates for any given percentile. These methods are quantitative. As indicated in Section 1.6, probabilistic methods can be applied to quantify variability only, uncertainty only, variability and uncertainty co-mingled, or variability and uncertainty that are distinguished. The first three are accomplished using “one dimensional” analysis, whereas the latter is accomplished using “two dimensional” approaches. For a one dimensional analysis, there is a unique value of any given variable associated with a percentile of the distribution. For example, there is a unique estimate of exposure at the 95th percentile of the distribution of inter-individual variability in exposure. For a two-dimensional analysis, for any given level of exposure there is a distribution regarding uncertainty as to what fraction of the population has equal or lower exposures. Conversely, for any
given percentile of the population, there is uncertainty as to the estimated exposure. Both one dimensional and two-dimensional methods are demonstrated in the case study of chapter 11.

5.2.3.1 – Statistical methods based upon empirical data

Statistical methods that are based upon analysis of empirical data are typically termed as “frequentist” methods, although sometimes the term “classical” is used (e.g., Warren-Hicks and Butcher, 1996; Morgan and Henrion, 1990; Cullen and Frey, 1999). However, the term “classical” is sometimes connotated with thought experiments (e.g., what happens with a roll of a die) as opposed to inference from empirical data (DeGroot, 1986). Therefore, we use the term “frequentist.”

Frequentist methods are fundamentally predicated upon statistical inference based upon long-run frequencies. For example, suppose that one wishes to estimate the mean emission factor for a specific pollutant emitted from a specific source category under specific conditions. Because of the cost of collecting measurements, it is not practically to measure each and every such emission source, which would result in a census of the actual population distribution of emissions. With limited resources, one instead would prefer to randomly select a representative sample of such sources. Suppose 10 sources were selected. The mean emission rate is calculated based upon these ten sources and a probability distribution model could be fit to the random sample of data. If this process is repeated many times, with a different set of ten random samples each time, the results will vary. The variation in results for estimates of a given statistic, such as the mean, based upon random sampling is quantified using a sampling distribution. From sampling distributions, confidence intervals are obtained. Thus, the commonly used 95 percent confidence interval for the mean is a frequentist inference based upon how the estimates of the mean vary because of random sampling for a finite sample of data.

Statistical inference can be used to develop compact representations of data sets (Box and Tiao, 1973). For example, a probability distribution model, such as a normal, lognormal, or other, can be fit to a random sample of empirical data. Examples of this are given in section 11.2.3. The use of probability distribution models is a convenient way to summarize information. The parameters of the distributions are subject to random sampling error and statistical methods can be applied to evaluate goodness-of-fit of the model to the data (Hahn and Shapiro, 1967). Goodness-of-fit methods are typically based upon comparison of a test statistic with a critical value, taking into account the sample size and desired level of significance (Cullen and Frey, 1999).

Frequentist statistical methods are powerful tools for working with empirical data. Although there appears to be a common misperception that one must have a lot of data in order to use frequentist statistics, in fact the fundamental starting point for a frequentist analysis is to have a random representative sample. Whether the data are a random representative sample depends on how the data were sampled, not on the sample size of the data. Representativeness (as defined in the glossary) implies lack of unacceptably large bias. If one needs
a random sample, and if the sample is not random, then it is also not representative. As long as this assumption is valid, it is possible to make statistical inferences even for very small data sets. The trade-off with regard to sample size is that the sampling distributions for estimates of statistics, such as the mean, distribution parameters, and others, become narrower as the sample size increases. Thus, inferences based upon data with small sample sizes will typically have wider confidence intervals than those based upon larger sample sizes.

The ability to make a judgment regarding representativeness of data is closely related to data quality issues. For example, representativeness is closely associated with the data quality issue of appropriateness. The data quality issue of accuracy and integrity is closely related to quantification or characterization of variability and uncertainty. The data quality issue of transparency pertains to clear documentation that, in turn, can provide enough information for an analyst to judge the representativeness and characterize variability and uncertainty.

In situations where the available data are not a random sample, then the analyst is forced to make a judgment as to whether to proceed with a frequentist analysis or not. It may be possible to stratify the data into groups each of which may more reasonably be assumed to be a random sample. For example, if a data set is comprised of a mixture of processes (e.g., different designs within an emission source category), then it would be appropriate if possible to separate the data with respect to the different designs and to analyze each design separately (Zheng and Frey, 2004). However, in some cases, the data are inherently biased with respect to an assessment objective. For example, suppose that one wants to quantify the outdoor ambient concentration to which adults are exposed when they are outdoors. Typically, available monitoring data are collected only at a sparse set of monitoring stations, and at altitudes that are not representative of the breathing zone. Thus, the uncritical use of such data could lead to biased inference as to the concentrations to which people are actually exposed at locations and altitudes different from those of the monitoring stations. In this situation, an air quality model could be calibrated to the monitoring data and used to interpolate (or extrapolate) to other locations and altitudes. However, there would be uncertainty associated with the model prediction, in addition to measurement uncertainty associated with the available monitoring stations.

Analysts often refer to data as being “limited”. In common, practical usage, the term “limited” might refer to any of several deficiencies, such as small sample size, lack of precision, lack of accuracy, or lack of knowledge of the pedigree of the data. These limitations are related to the data quality concepts of “accuracy” or “integrity”. Depending on the type of limitation, the data quality problems can translate into implications for uncertainty or can lead to a representativeness problem.

Some common situations that analysts face are the following:

- **Data are a random, representative sample** of the scenario and situation of interest. In this case, the analyst can use frequentist statistical methods;
• **Data are not random but are representative in other ways.** This may mean, for example, that the data are a stratified sample applicable to the real world situation for the assessment scenario of interest. In this case, frequentist methods can be used to make inferences for the strata that are represented by the data (e.g., particular exposed subpopulations) but not necessarily for all aspects of the scenario. However, for the components of the scenario for which the data cannot be applied, there is a lack of representative data. For example, if the available data represent one subpopulation, but not another, frequentist methods can be applied to make inferences about the former, but could lead to biased estimation of the latter. Bias correction methods, such as comparison to benchmarks, use of surrogate (analogous) data, or more formal application of expert judgment may be required for the latter;

• **Data are representative, but have other limitations.** The other limitations may include (for example) significant measurement errors leading to lack of accuracy and precision of each measurement. In the case of lack of accuracy of measurements, bias corrections gleaned from measurements of known quantities may be useful. In the case of lack of precision, there should be recognition that the variance of the sample of measurements may be significantly larger than the variance of the true variability in the quantity, because the observed variance includes contributions both from the true variability and the additional random error inherent in the measurement technique. Thus, methods for separating measurement error from inherent variability may be required (e.g., Zheng and Frey, 2005);

• **Data are numerous but not representative.** Data do not become more representative simply by having more data. If the data are not for the quantity of direct interest to the assessment, then the use of such data can lead to biased estimates regardless of the quantity of such data. Thus, a judgment is required (and should be explained) as to whether to use such data. If such data are used, then consideration (and explanation) should be given as to why they are selected for use, the possible biases associated with inferences from such data in the context of the analysis, and how such biases can be, or are, corrected in the assessment. For example, it may be known that the mean value is low because some benchmark data are available for comparison, or there are known omissions in the activity pattern or other characteristics that generated the data. In such cases, one might use the available data to gain insight into the relative range of variation compared to the observed mean value, but adjust the entire distribution to a different mean value using combinations of surrogate data, detailed analysis, or expert judgment.

In situations in which the data are not a representative sample, careful consideration needs to be given to the possibility of biases. A sample would be nonrepresentative, for example, if it was obtained for conditions or situations different from those that are assumed in the analysis. For example, suppose emissions were measured during steady-state full load operation, but that one desired to make predictions of emissions during transient part-load operation. The available sample of data is not representative of the desired scenario. If inferences are made based upon such data without any correction or
adjustment, it is possible that the mean emission rate will be biased and that the range of variation in emissions will be incorrectly estimated.

As Morgan and Henrion (1990) point out, for many quantities of interest in models used for decision making, there may not be a relevant population of trials of similar events upon which to perform frequentist statistical inference. For example, some events may be unique, or in the future, for which it is not possible to obtain empirical sample data. Thus, frequentist statistics are powerful with regard to their domain of applicability, but the domain of applicability is limited compared to the needs of analysts attempting to perform studies relevant to the needs of decision-makers.

5.2.3.2 –Methods for propagating variance or distributions through models

There are many methods and software available to assist the analyst in propagating information regarding probability distributions for inputs to a model in order to quantify key statistics of the corresponding distributions of model outputs. Here, we focus on methods that are quantitative and probabilistic. There are other quantitative methods that are not probabilistic, such as interval methods and fuzzy methods, as mentioned in Sections 5.2.1 and 5.2.2, respectively. In addition, the case study of chapter 11 mentions the factorial design method, which produces stratified quantitative estimates but does not produce a probability associated with each estimate. Chapter 11 also mentions the discrete probability distribution (DPD) method, which is a highly granular approximation of how to stratify the probability distribution of a model output into a small number of discrete ranges.

The key methods that are the focus of this section are categorized as analytical versus numerical methods. Analytical methods can be solved using explicit equations. In some cases, the methods can be conveniently applied using pencil and paper, although for most practical problems such methods are more commonly coded into a spreadsheet or other software. Analytical methods can provide exact solutions for some specific situations. Unfortunately, such situations are not often encountered in practice. Numerical methods require the use of a computer simulation package. They offer the advantage of broader applicability and flexibility to deal with a wide range of input distribution types and model functional forms, and can produce a wide variety of output data.

1) Analytical Methods. Analytical methods include exact solutions for specific situations, and approximate solutions that are applicable to a broader set of input distributions and model functional forms.

Exact analytical solutions can be obtained for summations of normal distributions. The sum of normal distributions is identically a normal distribution. The mean of the sum is the sum of the means of each input distribution. The variance of the sum is the sum of the variance of the inputs. Any statistic of interest for the output can be estimated by knowing its distribution type and its parameters. For example, for a model output that is a normal distribution with known parameter values, one can estimate the 95\textsuperscript{th} percentile of that output.
Similarly, exact solutions can be obtained for products (or quotients) of lognormal distributions (e.g., Burmaster and Thompson, 1995). This situation may be possible for some simple exposure assessments if one is working with one equation, such as the product of intake rate, concentration in the intake media (e.g., air, liquid), exposure duration, and exposure frequency, divided by an averaging time and body weight, as long as all of the input distributions are lognormal.

The exact solutions are not valid if any of the model inputs differ from the distribution type that is the basis for the method. For example, the summation of lognormal distributions is not identically normal, and the product of normal distributions is not identically lognormal. However, the Central Limit Theorem implies that the summation of many independent distributions, each of which contributes only a small amount to the variance of the sum, will asymptotically approach normality. Similarly, the product of many independent distributions, each of which has a small variance relative to that of the product, asymptotically approaches lognormality.

A method known as “transformation of variables” can be used to obtain exact analytical solutions in some situations other than those described here (Hahn and Shapiro, 1967), but is not used in practice. In practice, exposure models typically include both sums and products, such as for a multi-pathway exposure model. Furthermore, the inputs are not all of the same type of distribution. Also, there may be other complications, such as various types of dependencies among input distributions.

For more complex models or for input distributions for which exact analytical methods are not applicable, approximate methods might be appropriate. Many approximation methods are based on Taylor series expansion solutions, in which the series is truncated depending on the desired amount of solution accuracy and whether one wishes to consider covariance among the input distributions (Hahn and Shapiro, 1967). These methods often go by names like “generation of system moments,” “statistical error propagation,” “delta method,” and “first order methods,” as discussed by Cullen and Frey (1999).

The goal of approximation methods is to estimate the statistical moments of a model output based on the statistical moments of a model input. Such moments typically include the mean and variance, but can also include higher order moments related to skewness and kurtosis (flatness of the Probability Distribution Function (PDF)). Thus, these methods do not actually quantify specific percentiles of the model output distribution. Instead, the analyst can use the estimated moments for the model output to select an appropriate parametric distribution that approximates the unknown distribution of the model output, and then any statistic of interest can be estimated for the model output. The choice of an appropriate distributional approximation of a model output can be informed by the use of a “moment plane,” which is a display of regions of skewness and kurtosis that are characterized by specific types of distributions. For example, the normal distribution appears as a single point on such a plane, because it has only one possible shape. A lognormal distribution appears as a
line on a plot of kurtosis versus the square of skewness, because it can take on
many different magnitudes of skewness, and its probability distribution function
becomes increasingly “pointy” as the skewness increases (thereby increasing the
kurtosis). More details on the use of moment planes are given in Hahn and
Shapiro (1967) and Cullen and Frey (1999).

Approximation methods can be useful, but as the degree of complexity of the
input distributions or the model increases, in terms of more complex distribution
shapes (as reflected by skewness and kurtosis) and nonlinear model forms, one
typically needs to carry more terms in the Taylor series expansion in order to
produce an accurate estimate of percentiles of the distribution of the model
output. Thus, such methods are often most widely used simply to quantify the
mean and variance of the model output, although even for these statistics
substantial errors can accrue in some situations. Thus, the use of such methods
requires careful consideration, as described elsewhere (e.g., Cullen and Frey,
1999).

through models are typically preferred over analytical methods in practice
because they are versatile. Such methods can be used with a wide variety of
model functional forms, including large “black box” computerized models, and
for a wide variety of probability distributions used to present model inputs.
However, such methods require iterative evaluation of a model, which can be
computationally demanding. In some cases, it may not be feasible to do many
iterations with a particular model because of large run times for just one
iteration, not to mention hundreds or thousands of iterations. Of course, as
computing power increases with time, models that formerly seemed dauntingly
time consuming to run may be executable in minutes or seconds. Thus, the
feasibility of the application of numerical methods tends to improve over time,
although it also appears to be the case that as computing power increases, there
is a tendency to build bigger models.

The most commonly discussed numerical method for propagating distributions
through a model is Monte Carlo Simulation (MCS). MCS has been around for
over 50 years. In practice, MCS is based on generating a set of “pseudo-
random” numbers for each probabilistic model input. Pseudo-random numbers
should conform to an ideal of being statistically independent from one realization
to another and being a sample from a uniform distribution. They should not be
autocorrelated, and there should be no cycles or periodicity in the simulated
numbers. A good random number generator should be able to produce millions
or more such numbers before the cycle repeats. The sequence of numbers only
appears to be random; in fact, the same sequence can be reproduced by setting
the same “seed” values for the Pseudo-Random Number Generator (PRNG) each
time. Thus, it is possible to reproduce the same MCS at different points in time,
or to use the same series of random numbers to do comparisons between two
options or risk management alternatives.

MCS can involve several methods for using a PRNG to simulate random values
from the probability distribution of each model input. The conceptually simplest
method is the inverse-CDF method, in which each PRN represents a percentile of
the cumulative distribution function of the model input. The corresponding
numerical value of the model input, or fractile, is then sampled and entered into
the model for one iteration of the model. For a given model iteration, one
random number is sampled in a similar way for all probabilistic inputs to the
model. For example, if there are 10 inputs with probability distributions, there
will be one random sample drawn from each of the ten, and entered into the
model, to produce one estimate of the model output of interest. This process is
repeated perhaps hundreds or thousands of times to arrive at many estimates of
the model output. These estimates are used to describe an Empirical Cumulative
Distribution Function (ECDF) of the model output. From the ECDF, any statistic
of interest can be inferred, such as a particular fractile, the mean, the variance,
and so on. However, in practice, the inverse CDF method is just one of several
methods used by MCS software in order to generate samples from model inputs.
Others include the composition and the function of random variables methods
(e.g., Ang and Tang, 1984). However, the details of the random number
generation process are typically contained within the chosen MCS software, and
thus are not usually chosen by the user.

MCS is based on random sampling. Thus, it is possible to use frequentist
statistical methods to estimate confidence intervals for the simulated mean of a
model output taking into account the sample variance and the sample size.
Therefore, one can use frequentist methods to establish criteria for how many
samples to simulate. For example, one may wish to estimate the mean of the
model output within a specified precision. The number of iterations of the MCS
can continue until the simulation achieves convergence with the desired
precision. Alternatively, a user can make an initial run of an arbitrary sample
size, and then do statistical analysis of the output to determine if enough runs
have been made. If not, more runs can be made and combined with the data
from the first set of runs, until a large enough total sample size is obtained to
achieve the desired numerical precision for the model output. These types of
methods are described in more detail elsewhere (e.g., Morgan and Henrion,
1990).

However, a potential pitfall of MCS is to become fixated on achieving a high
degree of numerical simulation precision while losing sight of the quality of the
input data. For example, if an assessment is based on model input assumptions
for which there are key data quality limitations, it may not make sense to make
hundreds of thousands or millions of iterations in order to obtain a highly precise
numerical estimate of the model output. In some cases, analysts spend perhaps
too much time and effort worrying about achieving a high degree of precision for
the 99.9\textsuperscript{th} percentile of a model output, when the shape and parameters of the
model input distributions are not known with a high degree of confidence.

A commonly used alternative to MCS is \textit{Latin Hypercube Sampling} (LHS). LHS is
a stratified sampling method. In LHS, a choice must be made prior to starting
the simulation regarding the desired sample size. For each input, the probability
distribution is divided into the specified number of equal probability ranges,
according to the desired sample size. One sample is drawn from each of these
equal probability ranges. Thus, each range is sampled once without
replacement. Within each equal probability range, the sample can be based on
the median value, or can be chosen at random. The former is referred to as median LHS, and the latter as random LHS. One such sample is drawn for each model input that has a distribution, and one iteration of the model output is estimated. This process is repeated until all of the equal probability ranges of the inputs have been sampled. The advantage of LHS over MCS is that one can obtain a more stable and precise estimate of the ECDF of the model output in a smaller number of model iterations than for MCS. However, because LHS is not a random sampling method, frequentist sample statistical methods cannot be applied to characterize the precision of the output or to assist in choosing a sample size. However, ordinal statistical methods can be of some assistance in these regards (e.g., Morgan and Henrion, 1990). A potential pitfall of LHS is that there may be spurious correlations among the model inputs unless a restricted pairing method is used to choose the order in which samples are drawn from the equal probability strata of each input distribution. However, numerical methods for imposing independent sampling, or for inducing a specified rank correlation between two or more inputs, are available (e.g., Iman and Conover, 1982).

5.2.3.3 – Statistical methods based upon judgment

An alternative to the frequentist approach to statistics is based upon the use of probability to quantify the state of knowledge (or ignorance) regarding a quantity. This view is known as the personalist, subjectivist, or Bayesian view (Morgan and Henrion, 1990). For consistency throughout the text, we will use the term “Bayesian.” Unlike a frequentist, a Bayesian does not require assumptions about repeated trials in order to make inferences regarding sampling distributions of statistical estimates (Warren-Hicks and Butcher, 1996). Bayesian methods for statistical inference are based upon sample information (e.g., empirical data, when available) and a prior distribution. A prior distribution is a quantitative statement of the degree of belief a person has that a particular outcome will occur. For example, an expert might express a judgment regarding the distribution of fish consumption for a village comprised of subsistence fisherman, based upon logical inferences or analogies with other data (e.g., Cullen and Frey, 1999). Because the prior distribution, expresses the state of knowledge of a particular expert (or group of experts), this distribution is conditional upon the state of knowledge. Methods for eliciting subjective probability distributions are intended to produce estimates that accurately reflect the true state of knowledge and that are free of significant cognitive and motivational biases.

Morgan and Henrion (1990) provide a useful introduction to the potential pitfalls of eliciting expert judgment regarding distributions and regarding expert elicitation protocols that are designed to overcome or minimize such pitfalls.

The cornerstone of Bayesian methods is Bayes’ Theorem, which was first published in 1763 (Box and Tiao, 1973). Bayes’ Theorem provides a method for statistical inference in which a prior distribution, based upon subjective judgment, can be updated with empirical data, to create a “posterior” distribution that combines both judgment and data. As the sample size of the data becomes large, the posterior distribution will tend to converge to the same
result that would be obtained with frequentist methods. In situations in which there are no relevant sample data, then the analysis can be conducted based upon the prior, without any updating.

Although Bayesian methods are attractive with regard to their capability to accommodate information based upon both data and judgment, there appear to be several reasons for the lack of more widespread use of these methods, as described by Smith et al. (1996). Bayesian analysis is complex and requires considerable judgment and choices pertaining to prior distributions, and modeling approaches. Further, software is needed to deal with complex integrations. Smith et al. (1996) argue that the frequentist methods are practical and relatively simple, although certainly there can be complex frequentist methods of inference that require judgment and software to implement.

Other often cited drawbacks of Bayesian methods are that they are inherently subjective and therefore there is the potential for lack of consistency or replicability, particularly if the same analysis is repeated by different groups that obtain judgments from different experts. In response, proponents of Bayesian methods typically argue that, in such situations, frequentist statistical inference cannot be applied. Although differences in judgment are to be expected among experts, sensitivity analysis methods can be used to assess whether such differences have a significant impact on the results of the analysis. If they do, then it is useful to pinpoint the source of disagreement for purposes of informing the decision maker or to develop a research program to collect data upon which such differences can be resolved.

While the Bayesian approach explicitly acknowledges the role of judgment, the frequentist approach also involves judgment regarding the assumption of a random, representative sample, selection of probability models, evaluation of models using specific goodness-of-fit or diagnostic checks, and other steps in analysis (e.g., Cullen and Frey, 1999).

Thus, despite its limitations, the Bayesian approach is more flexible in dealing with situations in which data are limited or not available, but in which the state of knowledge is adequate to support judgments regarding prior distributions.

5.2.4 – Sensitivity analysis
Sensitivity analysis quantifies the variation in model output that is caused by specific model inputs. As such it can be used as an underlying basis for uncertainty analysis as well as for supplying supplemental information (e.g., Saltelli et al., 2000; Cullen and Frey, 1999). Sensitivity analysis can be used to answer the following types of questions (Mokhtari and Frey, 2005):

- What is the rank order of importance among the model inputs?
- Are there two or more inputs to which the output has similar sensitivity, or is it possible to clearly distinguish and discriminate among the inputs with respect to their importance?
Which inputs are most responsible for the best (or worst) outcomes of the output? Is the model response appropriate?

Sensitivity analysis can be either qualitative or quantitative. In a qualitative analysis, the assessor identifies the uncertainties affecting the assessment and forms a judgement of their relative importance. Such an evaluation is implicit in the qualitative approaches to assessing uncertainty, described in Section 5.1. This is subjective and therefore less reliable than a quantitative sensitivity analysis. However, it is a practical first step for identifying the most important uncertainties as a focus for quantitative analysis.

Quantitative methods of sensitivity analysis and metrics for measuring sensitivity are widely available. The most commonly used sensitivity analysis methods are often relatively simple techniques that evaluate the local linearized sensitivity of model response at a particular point in the input domain. This type of approach is typically used if the model inputs are treated as point estimates, often representing the “best guess” as to the true but unknown value of each input. The sensitivity analysis of point estimates is often done for the purpose of evaluating how much the model would respond to a unit change in the input. One example is the use of partial derivatives. A simple variation on this approach is to vary each input individual over a possible range of its values, rather than just for a small perturbation or a change of only one unit of measure. Although conceptually simple, local sensitivity-analysis techniques typically suffer from two key shortcomings: (1) they do not take into account the simultaneous variation of multiple model inputs; and (2) they do not take into account any nonlinearities in the model that create interactions among the inputs.

If uncertainty analysis is thought of as a forward propagation of distributions through the model, then sensitivity analysis could be conceptualized as looking back from the output to the inputs to determine which of the inputs is most important to the range and likelihoods of the final result. For a probabilistic analysis based upon Monte Carlo simulation, a variety of statistically-based methods can be used to ascertain what portion of the variation in the model output can be attributed to each of the model inputs. Depending on the functional form of the model, the resulting measures of sensitivity may be exact or may be approximate; however, even in the latter situation they are typically highly informative with regard to management and planning needs. For example, because uncertainty arises from lack of perfect knowledge of the true but typically unknown value of actual emissions, uncertainty can be reduced by obtaining better information. Therefore, insights regarding key sources of uncertainty can be used to assess priorities for collecting additional data or information in order to reduce uncertainty. Sensitivity analysis is typically used to (1) assist in verification/evaluation of models, (2) identify key sources of variability and uncertainty; and (3) evaluate the importance of key assumptions during model development (Russel and Dennis, 2000).
(2002) classify sensitivity analysis methods with regard to characteristics as mathematical, statistical and graphical methods. Saltelli et al. (2000) classify sensitivity analysis methods with respect to the application and scope as screening, local, and global. The former approach is used here.

Examples of mathematical methods include Nominal Range Sensitivity Analysis (NRSA) (Cullen and Frey, 1999) and Differential Sensitivity Analysis (DSA) (Hwang et al., 1997). Examples of statistical sensitivity analysis methods include sample (Pearson) and rank (Spearman) correlation analysis (Edwards, 1976), sample and rank regression analysis (Iman and Conover, 1979), Analysis Of Variance (ANOVA) (Neter et al., 1996), Classification And Regression Tree (CART) (Breiman et al., 1984), Response Surface Method (RSM) (Khuri and Cornell, 1987), Fourier Amplitude Sensitivity Test (FAST) (Saltelli et al., 2000), Mutual Information Index (MII) (Jelinek, 1970), and Sobol’s indices (Sobol, 1993). Examples of graphical sensitivity analysis methods include scatter plots (Kleijnen and Helton, 1999) and conditional sensitivity analysis (Frey et al., 2003). Further discussion of these methods are provided in Frey and Patil (2002) and Frey et al. (2003, 2004).

Sensitivity analysis methods can be used in combination with methods for variance propagation. For example, Cullen and Frey (1999) describe how variance in the sum of random numbers can be apportioned among the inputs to the sum. All of the statistical sensitivity methods mentioned above can be applied to the results of MCS, in which simulated random values are available for a model output and each probabilistic model input. FAST is an alternative method for both propagating distributions through a model as well as estimating the contribution of each input to the variance of the output based on a specific type of sensitivity index. Sobol’s method requires some additional simulations but can be implemented in the context of MCS. Guidance on how to choose sensitivity analysis methods for application to risk-related problems is given by Mokhtari and Frey (2005) and Frey et al. (2004).

**Recommendation 6:**

Sensitivity analysis should be an integral component of the assessment. The results of sensitivity analysis should be used iteratively as part of the exposure variability and uncertainty assessment to help prioritize the development of quantitative estimates of variability, uncertainty, or both. The results of sensitivity analysis should be used to provide insight regarding the importance of different sources of variability, uncertainty, pathways, and other factors of importance to the assessment.

### 5.3 – Data and Resource Requirements

Human exposure assessments require data and models to address a number of key relationships. Here we consider the requirements for data for establishing both the structure and the numerical value of these links. Human exposures to environmental emissions include at least five important relationships which will demand data, modeling, and evaluation resources:
1. the magnitude of the source medium concentration, that is, the level of contaminant that is released to indoor or outdoor air, to soil, water, etc. or the level of contamination measured in or estimated in the air, soil, plants, and water in the vicinity of the source;

2. the contaminant concentration ratio, which defines how much a source-medium concentration changes as a result of transfers, degradation, partitioning, bioconcentration, and/or dilution to other environmental media before human contact;

3. the level of human contact, which describes (often on a body-weight basis) the frequency (days per year, minutes per day, etc.) and magnitude (m$^3$/h air breathed, kg/day food ingested, m$^2$/h surface contacted, etc) of human contact with a potentially contaminated exposure medium;

4. the duration of potential contact for the population of interest relating to the fraction of lifetime during which an individual is potentially exposed;

5. the averaging time span for the type of health effects under consideration; that is, one must consider the appropriate averaging time span for the cumulative duration of exposure such as a human lifetime (which is typical for cancer and chronic diseases) or some relatively short time span (in the case of acute effects).

These factors typically converge as a sum of products or quotients to define a distribution of population exposure or a range of individual exposures. The reliability of population exposure estimates will depend strongly on the quantity and accuracy of the obtainable data associated with these five links.

5.4 – Interpretation of Results

The interpretation of uncertainty analysis results can cover a wide range of issues. Here, we consider the interpretation of results with regard to the needs of decision makers who would use the results of uncertainty analysis in exposure assessment. The discussion is primarily based upon Morgan and Henrion (1990), Thompson and Graham (1996), and Bloom et al. (1993). The discussion is organized on the basis of key questions that decision makers often ask, as reported by Bloom et al. (1993) based upon a survey of senior risk managers at the U.S. Environmental Protection Agency, and as described by Thompson and Graham (1996).

What is the distribution of exposures among different members of an exposed population?

This question is based upon the premise that each individual in an exposed population is expected to have different exposures because of inter-individual variability in exposure factors, such as intake rate and activity patterns. If there are substantial differences in exposures among members of an exposed population, then one might identify subpopulations that tend to be more highly exposed and focus the development of exposure reduction policies for these
groups. For example, because of differences in inherent characteristics or in activity patterns, some groups such as children or the elderly may be more highly exposed or more susceptible to adverse effects as a result of exposures. Thus, the analysis could be stratified to focus on such groups. Inter-individual variability in exposures may raise concerns about equity.

How precise are the exposure estimates?
This question focuses on the simultaneous, combined effect of uncertainties in all exposure factors with respect to overall uncertainty in the exposure assessment. This question can be answered by propagating uncertainty estimates for exposure model inputs through the exposure model. Typically, this question could be answered in terms of absolute or relative ranges (e.g., a 95 percent probability range of plus or minus 25 percent of the exposure for a particular percentile of inter-individual variability), based upon estimates of uncertainty for a particular percentile of the exposed population.

How precise do exposure estimates need to be?
The required degree of precision of an estimate will vary depending upon its intended use. For example, the degree of precision expected of a refined exposure analysis that accounts for inter-individual variability is typically higher than that for a conservative screening analysis based upon upper bound assumptions. Furthermore, the desired precision (or lack of uncertainty) would depend on whether the range of uncertainty is large enough to cause ambiguity regarding the preferred decision. In this latter case, ideally it would be desirable to reduce uncertainty by collecting more data or information. On the other hand, some decisions may need to be made before uncertainties can be further reduced. Thus, the desirable precision might be a long-term goal but not achievable in the time frame required for a near-term decision. Recognition that management of exposure problems can be iterative and adapted over time is one strategy for reducing uncertainties in the longer-term.

What is the pedigree of the numbers used as input to inventories?
This question deals with issues of who developed the numbers, how they were developed, and who has reviewed them. For example, have they been subject to scientific peer review? Are the numbers based upon measurements or are these preliminary estimates based upon the judgment of an analyst? The decision maker is interested in the degree of confidence assigned to a number. In the context of emission inventories, this relates to concerns over whether the data were obtained using approved or acceptable measurement techniques and whether they pertain to a random representative sample of emission sources. Alternatively, data may have been obtained using a variety of measurement methods that may not be directly comparable, and might be for non-representative conditions. Thus, the data may be “bad” in some way or incomplete.

What are the key sources of uncertainty in the exposure assessment?
This question can also be posed as: Which exposure factors contribute the most to the overall uncertainty in the inventory? This insight can be used, in turn, to target resources to reduce the largest and most important uncertainties. There are various ways to answer this question, including various forms of sensitivity.
analysis. For example, in the context of a probabilistic uncertainty simulation for an overall exposure assessment, various statistical methods can be used to determine which input distributions are responsible for contributing the most to the variance of the output.

**How should efforts be targeted to improve the precision of exposure estimates?**

Knowledge of key sources of uncertainty in exposure estimates helps guide additional data collection to reduce uncertainty in order to improve the precision of the estimates. For example, the identification of key sources of uncertainty can be used to prioritize information-gathering efforts for the most important inputs. Because uncertainty results from lack of knowledge, an effective approach to its reduction is to obtain more knowledge, through additional measurements or the development of more precise and accurate measurement methods.

**How significant are differences between two alternatives?**

This question pertains to determining whether it is possible to discriminate between two alternative estimates even though they are both uncertain. For example, when comparing exposure reduction strategies, does one offer a high confidence of a real exposure reduction compared to a baseline even though both the estimates of baseline and controlled exposures are subject to uncertainty? This question can be answered by estimating the probability distributions for differences in exposures.

**How significant are apparent trends over time?**

One approach for answering this question is to evaluate the statistical significance of changes over time, or to determine whether a time-series model could be used to describe data and, therefore, to gain insight regarding stationarity (or lack thereof) of the series, as well as its cycles and seasonality. Stationarity refers to a situation in which the mean and other statistics do not change as a function of time. Cycles and seasonality refer to periodicity in the time series such as diurnal or annual effects. Comparisons of distributions for specific points in time (e.g., comparison of weekday versus weekend ambient concentrations) can also provide insight into temporal trends. For example, a probability distribution of the change in emissions from one time period to another can be used to assess the probability that emissions have increased or decreased, and the likelihood of various magnitudes of the change.

**How effective are proposed control or management strategies?**

This question could pertain to the confidence with which a standard will be met. For example, Hanna *et al.* (2001) assess the uncertainty associated with estimates of predicted ambient ozone levels subject to a particular emission scenario, and Abdel-Aziz and Frey (2004) evaluate the probability of noncompliance with National Ambient Air Quality Standards (NAAQS) for ozone based upon uncertainty in emission inventories which are propagated through an air-quality model. A probability distribution of estimated exposures can be compared with a point estimate of an exposure benchmark in order to determine the probability that the benchmark will be exceeded and, if so, by how much.
Is there a systematic error (bias) in the estimates?

Systematic error, or bias, typically occurs when inferences are made on the basis of data which are not representative of the real world situation for which an estimate is desired. For example, to estimate the inhalation exposures for ambient air pollution caused by power plant emissions, one has to define a scenario. The scenario might focus on actual operations of power plants for a specific time period (e.g., one year) for a particular geographic area (e.g., a state or a province). In order to estimate exposure for this scenario, one should have data representative of the particular mix of power-plant designs, fuels, operating practices, loads, and ambient conditions. However, if data are available only for full-load operation of plants which differ somewhat in design, fuel, operation, and ambient conditions, then the average emission factor derived from the available data may differ from the true population average for the scenario of interest. The question regarding whether systematic error exists is difficult to answer in the absence of an independent basis for comparison of the estimate with some type of a “ground-truth” or “reality check.” However, it is possible to incorporate expert judgments regarding sources of bias.

Is there ongoing research that might fill critical data gaps within the near term?

This question, and many of the others, is fundamentally motivated by the desire not to be unpleasantly surprised or overtaken by events. For example, if new research might resolve some of the key uncertainties in the assessment, is it worth waiting until that information is available before making a decision?

Are the estimates based upon measurements, modeling, or expert judgment?

This question pertains to the pedigree of information used to support the assessment. While there is typically a preference for estimates based upon directly relevant measurements, the use of models and judgments may be justified when relevant data are not available. For example, available data may not be representative and thus inferences based upon them may lead to biases. Moreover, there may be gaps in available data such that it is not possible to make empirically based estimates for some inventory inputs that might be critical to the assessment. In such cases, inferences could be made based upon indirect evidence (e.g., by interpolation, extrapolation, or the use of theoretical hypotheses using models, or elicitation of judgment regarding subjective probability distributions for the inputs to an analysis, or both).

The preceding identification and discussion of key questions posed by decision makers highlights the importance of identifying and characterizing uncertainty in emission inventories. The broad range of questions illustrates the importance of knowing what questions must be answered before developing inventories and estimates of their uncertainties. Some sources of uncertainty, such as possible sources of bias and problems with lack of data, may have to be dealt with qualitatively (e.g., by listing caveats or by using qualitative ratings) or by using expert judgment as the basis for quantifying subjective probability distributions. Other sources of uncertainty may be amenable to quantification using statistical methods based upon analysis of empirical data. Later sections of this chapter provide an overview of these methodologies. Furthermore, uncertainty analysis
can be supplemented with sensitivity analysis in order to identify key sources of uncertainty for purposes of prioritizing activities that could reduce uncertainty.

5.5 – Use of Uncertainty Analysis in Evaluation and Validation

Based on the U.S. EPA Committee on Regulatory Environmental Models (CREM), model (or data) evaluation “is the process for generating information over the life cycle of the project that helps to determine whether a model and its analytical results are of a quality sufficient to serve as the basis for a decision. Model quality is an attribute that is meaningful only within the context of a specific model application. In simple terms, model evaluation provides information to help assess the following factors: (a) How have the principles of sound science been addressed during model development? (b) How is the choice of model supported by the quantity and quality of available data? (c) How closely does the model approximate the real system of interest? (d) How well does the model perform the specified task while meeting the objectives set by quality assurance project planning?”

In the context of evaluation, an uncertainty analysis “investigates the effects of lack of knowledge and other potential sources of error in the model (e.g., the “uncertainty” associated with model parameter values) and when conducted in combination with sensitivity analysis allows a model user to be more informed about the confidence that can be placed in model results.” [Pascual et al., 2003].

Validation is the process by which the reliability and relevance of a particular approach, method, or assessment is established for a defined purpose (WHO, 2004). Uncertainty analysis can contribute to this, by indicating the reliability of the exposure estimate (how different the true exposure might be) and hence its usefulness for decision-making.

An especially useful form of validation is where the results of an assessment can be compared with independent data or information, e.g. comparing predicted exposure with biomarker measurements or epidemiological studies. When making such comparisons it is important to remember that both sides of the comparison are subject to uncertainty. The methods described in this document should be applied to the independent data, as well as to the exposure assessment, to provide a fair comparison between the two.

5.6 – Summary of Characterization Methods

Methods available for analysing uncertainties fall into 3 broad types: qualitative, deterministic, and probabilistic. They provide contrasting ways of characterising the relative importance of the uncertainties affecting an assessment, and of characterising the overall uncertainty of the assessment output, and provide an essential input for decision-making.

In general, probabilistic approaches require more expertise and time than deterministic and qualitative approaches. For this reason, it is efficient to adopt a tiered approach, which starts by considering all uncertainties qualitatively (Tier 1). This may be sufficient, if the outcome is clear enough for risk managers to
reach a decision. Otherwise, the uncertainties that appear critical to the outcome may be analysed deterministically (Tier 2) or probabilistically (Tier 3) as shown in Table 4.1.

A range of alternative methods exists at each tier, each with their own advantages and disadvantages. Although there is substantial experience with uncertainty analysis in some fields (e.g., climate change), it would be premature to make prescriptive recommendations on which methods to use in exposure assessment. For example, when discussing the use of probabilistic methods for microbial risk assessment, the former EC Scientific Steering Committee concluded that “a quick harmonisation at the present state-of-the-art should be avoided” (European Commission, 2003). The same is true of qualitative approaches. Instead, it is desirable to maintain a flexible approach, selecting the most suitable methods for each assessment (e.g., Mokhtari and Frey 2005). More guidance and harmonization may be possible in the longer term, as further experience accumulates.

6 – Communication
Communication about exposure and risk is difficult, partly because the information that needs to be communicated is sometimes complex, and partly because perception and evaluation of risk is influenced by a range of other factors including the context and preconceptions of the audience. The aim of risk communication should be to supply people with the information they need to make informed decisions about risks to their health, safety, and environment (NRC 1996). Furthermore, it is generally necessary for those performing exposure assessment to communicate with several different audiences who each require different communication formats, for example, scientists, decision-makers, media and the lay public. People process information within the context of their existing “mental models” (Morgan et al. 1992) and beliefs. Dealing with exposure assessment models and corresponding results at the same time as communicating the inherent uncertainties makes the task complex. Terms such as variability between individuals, uncertainty about appropriate scenarios, models and data, as well as aspects of confidence in communication partners play a central role.

6.1 – Introduction and historical background
The process of risk assessment was first formalized (NRC 1983) by the U.S. National Academy of Sciences through its U.S. National Research Council in 1983. The three stages of risk analysis are defined as: risk assessment, risk management and risk communication. The important principle is the functional and organisational separation of exposure and risk assessment from risk management to avoid any non-science driven influences on the assessment procedures. However, many interactive elements are essential for a systematic risk assessment and management process. The risk management process is illustrated as a circular process (PCC 1997). At a governmental level it is often called “the risk management process”, where the inner part of the circle may contain communication and learning elements (e.g., Strategy Unit 2002, p.44).
When communicating (writing, talking or keeping silent) about uncertainty in exposure and risk assessment, it is necessary to reveal the status of inherent uncertainty with respect to expertise, to the assumptions and the models/data used in exposure assessment.

What is needed for risk communication is a conceptual framework (Covello and Merkhofer 1993) that includes at least (a) a convenient language for communication between risk assessors and risk managers, (b) a means for clarifying similarities and differences in the capabilities, applicabilities, input requirements, and analytical perspectives of different assessment methods and possible consequences of restrictions, (c) a means for identifying adequate and effective methods for analysing exposure problems, and (d) an aid in identifying weak links in the sequence of the exposure assessment process.

![Figure 6.1. Risk Assessment and Risk Management (PCC 1997, modified)](image)

The NRC (1989) defines risk communication as an interactive process of information exchange between individuals, groups and institutions. It mostly includes statements, news and messages about the nature of risks, fears and anxiety, opinions, reactions with respect to risk statements and institutional forms of risk management. Risk communication does not end at the departure gate of organisations. It is driven by a large set of attributes which influence the risk perception and the reaction to risks (Brehmer 1987, IRGC 2005): personal control, voluntary versus involuntary, habituation to the risk, dread (sequence of events) of the risk, ability of perceptual recognition of the risk, irreversibility of the consequences, unfair distribution of risks and benefits, natural origin versus manmade risks, identification of the person or organisation (blame) causing the risk and trust in risk regulation organisations/institutions.

Mainly in response to the anthrax attacks in the U.S., in 2002 the Center for Disease Control and Prevention (CDC) published a report on “Crisis and Emergency Risk Communication” (Reynolds 2002). The report illustrates two prerequisites for successful risk communication: credibility and trust. These two
elements (Figure 6.2) may be highly important when dealing with uncertainty in exposure and risk assessment (Sjöberg 2001). The prerequisites for credibility are accuracy of information and speed of release; the main attributes of trust are empathy and openness.

**Figure 6.2.** Elements of a successful communication (Reynolds 2002, modified)

Accuracy of information is a result of scientific expertise, the delivery of adequate, complete and unbiased information about results and residual uncertainties. The speed of release is influenced by the organisational culture, to what extent the process to find answers and to acknowledge uncertainties is developed. Empathy is related to the willingness to recognize the situation (the scenario) in which the persons/clients are. The degree of openness corresponds to the information given about uncertainties and limitations in the exposure assessment, the restrictions with respect to selected scenarios, the model assumptions and parameters for the target population, mainly the degree of possible over and under-estimation. These aspects correspond directly to the main characteristics of uncertainty discussed in section 5.1.4.: the appraisal of the knowledge base (section 5.1.4.2) and the subjectivity of choices (section 5.1.4.3). As in any applied science, trust in the credibility of scientists dealing with complex systems (Jungermann et al. 1995) is a major influence factor for acceptance of the results.

6.2. The position of exposure and uncertainty assessment in the risk communication process

The product of the exposure assessment process should provide the scientific basis for risk management and communication which is often initiated by identifying possible hazards. As a measurement, the result is only complete when accompanied by a quantitative statement of its uncertainty (NIST 1994). Uncertainty is required in order to decide whether the result is adequate for its intended purpose and to ascertain whether it is consistent with other similar results. In 2002, the European Commission’s Health and Consumer Protection Directorate published a scheme in a report on animal health which highlights the position of exposure assessment and emphasizes the need for risk communication in all steps of risk assessment (Figure 6.3).
Risk characterisation has a central position in the linkage of facts about the hazards, the choice of adequate exposure scenarios, data and assumptions, resulting in exposure calculations. The results and their inherent uncertainties give the input to the risk and consequence assessment. The risk and uncertainty assessment is intended to give “complete information to risk managers, specifically policy-makers and regulators, so that the best possible decisions are made” (Paustenbach, 1989 p.28). Thus the inherent uncertainties in exposure assessment will have a high impact on the management of risks. Morgan and Henrion (1990) divides those involved in the assessment and communication process roughly into groups that are (a) substance-focused, who try to obtain answers to formulated questions, develop insight and understanding, (b) position-focused, who provide arguments, substantiation and generate answers for justification, (c) process-focused, who persuade others that things are under control, organisations fulfil laws and expectations and (d) analysis-focused, who seeks professional enjoyment, reward and development of analytical techniques. Communication partners might differentiate their attitude towards or against scientists doing the exposure assessment in a similar manner (Frewer et al. 1996).

**Figure 6.3.** Risk characterisation as a core element in risk communication (EC 2002, modified)

6.2.1 Uncertainty in exposure assessment as a prognostic technique

Exposure assessment is done under the strong assumption that (a) an adequate model for exposure calculation is on hand and (b) that sufficient data about all influential exposure factors is available. The calculation is a prognosis about the
expected level of exposure or the burden. Direct methods of exposure
assessment like personal sampling (air, radiation), duplicate studies (nutrition)
or human biomonitoring provide information on a measurement level. The
exposure assessors and the risk managers should balance the reasons for using
prognostic techniques instead of direct exposure measurement methods. Both
should anticipate critical questions about the validity of the exposure assessment
technique in the course of public risk communication. Questions heared by the
authors from concerned persons like

- “How sure are You about ….?”,
- “What about the statement of the scientist …. , who argues ….?”,
- “Did You ever prove before that your method works well?”,
- “What does your method/results mean for me/my family?”,
- “What would be the result if you use your sophisticated model for me?”,
- “Why do You use national reference data for us, aren’t we different ….?”
- “Your data seems to be fairly old fashioned, doesn’t the situation/product
change?”

All questions deal with relevant aspects of uncertainty. The important criterion
common to all these questions is the degree of structural and predictive validity
(Shylakhter 1994) of the exposure assessment.

An argument often heard in administrative units in favour of exposure
assessment in contrast to biomonitoring and epidemiology is “time and costs”,
although it has a low impact in convincing the public, the media and other
scientists. If the methods of exposure assessment have not been extensively
evaluated previously, if they are new as a field application, or if they have not
been reviewed in an organized scientific process, doubts about the certainty,
validity and objectivity should be admitted. A high level of scientific agreement
is necessary for an exposure assessment approach to reach a concrete situation
which is modeled by a given exposure scenario (WHO 1999). Model based
exposure assessment is only one, normally the fastest and often the only
possible step to achieve some degree of knowledge, but it uses a prognostic
technique with inherent uncertainty.

6.2.2 From scenario definition to uncertainty analysis: communication
with the risk managers
For the risk communication process it is necessary that the selected scenarios for
which an exposure assessment is conducted should be in complete agreement
with the ordering management and the given task. Restrictions and limitations
should be discussed and documented. Choosing a very broad scenario might
lead to a lack of precision for subgroups; selecting specific groups (e.g.
stratification for children, consumer habits) will result in specified models which
might not be compatible with an approach for the general population. Each
supplementary analysis of the possible effects of changing the scenario, the age
groups, populations characteristics and the model structure might show specific
uncertainties, but together they secure the overall result.
The calculated exposure results are expressed in the language of numbers. The level of uncertainty is described qualitatively or quantitatively. A numerical approach has the advantages of precision, leaving less room for misinterpretation and providing more input for the decision maker (Covello and Merkhofer 1993).

Although we prefer numerical descriptions, there is a great difference between using numbers for individual predictions for persons or as an average or quantile related estimate for the description of groups. In risk communication both figures must be distinguished clearly; the first points to individuals, the second to aggregates (groups, communities, populations). Communication with individuals requires an individual prediction of exposure and perhaps an exposure characterization (distribution or range) of the total population for comparison. Uncertainties that might be topics of discussion are exposure events and history, day-to-day-variation, questions of the inclusion of all exposure routes and pathways. For communication with groups, the presentation of the exposure assessment should mainly reflect the variability over persons and subgroups.

"Take away variety and nothing remains but averages with zero standard deviations and central tendencies always on the mark. Take away variety, in other words, and we eliminate uncertainty... But the sum and substance of risk management is in the recognition of variety." (Bernstein 1996).

Managers, especially those from regulatory and administrative units, seem to prefer verbal conclusions and statements in a qualitative form. This is not based on a general dislike for numbers, rather their task is driven by questions like “Is there enough safety for the total population or for special groups?”, “Should we expect to see an exposure higher than an acceptable/legitimate level?” or “Does the exposure and risk analysis give rise to exposure reduction actions, warnings, consumer advice or prevention programs?”. All these questions contain qualities instead of quantities and they include an evaluation of the results (and the reported uncertainty). A tiered approach with a two-dimensional Monte Carlo uncertainty analysis is useful for separating the uncertainty into uncertainty due to population variability, measurement errors as well as uncertainty due to lack of knowledge. Knowing where the main contributions to uncertainty stem from allows risk managers to allocate calculated resources for the reduction of uncertainty efficiently.
Figure 6.4. The relationship between the three components of risk analysis (WHO 2005)

As a consequence of different demands risk managers and interested groups sometimes tend to answer by simplifications that are not acceptable to those doing exposure, uncertainty and risk assessment. These answers inevitably imply a value judgement about the significance or acceptability of the exposure. To provide this goes beyond the scope of exposure assessment in two important ways (Figure 6.4): First, you cannot judge the significance of exposure without considering the dose-response-relationship and second, you cannot decide on acceptability or the need for management action without balancing the predicted effects against other factors such as cost, benefits, new risks induced by action/reaction, social values, feasibility of control/enhancement actions, etc. The Codex working principles for risk analysis also say explicitly that it is the job of the risk manager to resolve the impact of uncertainty on decision-making, and that uncertainty should be quantified as far as scientifically achievable. So in our context that implies that the output of the exposure assessment should - as far as possible - be quantitative. We also need to say how to communicate those uncertainties that we are unable to quantify, and this has to be done in such a way that the decision-maker can weight these unquantified uncertainties (see 6.3.3) together with the quantified ones (see 6.3.2).

Using default values, the selected range of the influencing variables must be chosen well, as the complaint of any particular person “You have not considered that for me/my family the exposure (this influence factor) is higher than that you have used!” might devaluate the whole exposure assessment in a public debate. Furthermore, the authors’ experience shows that it is much better to use distributions for the influence factors. Considering combinations of distributions for the input variables might lead to answers like “We have considered (foreseen) your situation. Your personal situation is included in the expected variability.” or “The calculation is done as a possible combination of all (including the possible but unwanted) conditions”.

Sensitivity and extremal value analysis as well as an analysis of variance propagation might lead to deeper insight into the exposure process. Especially these steps of exposure analysis might have a high value for risk management, as they identify the most influential factors and routes for high exposure circumstances. A sensitivity analysis might clarify which influence the variance
within each variable has on the variance of the target variable. If variables prove to show a low sensitivity, the influence of existing uncertainty in these variables on the result (e.g., low sample size, no knowledge of the distribution type and parameters) will be low. Risk managers will look first and foremost at variables that might be influenced (exposure frequency, concentrations). The results of a well-conducted sensitivity analysis might direct lead directly to recommendations for exposure reduction or prevention measures, which might be justified by the state of knowledge (model) and facts (input data). Sensitivity analysis is particularly useful for an identification of the main exposure sources as well as for the selection of possible actions. It reduces uncertainty in decision making. The knowledge gained in this step of uncertainty analysis might have a high profit in risk communication.

All this is easily written but hard and time consuming work to do. If “time until a first answer should/must be given” is a constraint or the “speed of release” is a critical dimension (Reynolds 2002), then simplification is inescapable. The degree of uncertainty in exposure estimates consequently increases. It is the responsibility of exposure assessors to inform risk managers about the possible consequences of any simplification and reduction of complexity in the uncertainty of the results and the restrictions towards the generalisability of results. From the point of a risk manager, this might result in a crucial conflict with the exposure assessors. The result of an adequate exposure assessment includes a numerical estimate, a sensitivity analysis, an evaluation and an explanation of uncertainties. This takes time. The responsible risk manager has to decide early on the necessity of actions. Horton’s paper (1998) on the precautionary principle points to this conflict:

“We must act on facts, and on the most accurate interpretation of them, using the best scientific information... That does not mean that we must sit back until we have 100% evidence about everything. Where the state of the health of the people is at stake, the risks can be so high and the costs of corrective action so great, that prevention is better than cure. We must analyse the possible benefits and costs of action and inaction.”

Consequently, risk managers, as transmitters of information to the public, want to avoid vagueness and press for precise statements (without uncertainty); as otherwise they must decide and act under uncertainty. One task of the exposure assessment step is to articulate the main arguments for restrictions with respect to the interpretation together and propose what could and should be done to enhance the scientific basis for a refined analysis which would result in less uncertainty.

6.2.3 – Anticipating the demands of the audiences

The NRC (1989) defined the group of players as individuals, groups and institutions. The WHO report on food safety (1995) focuses mainly on organisational interaction “… among risk assessors, risk managers, and other interested parties”. Risk communication is done on all levels of interaction. In each situation there might be a different assembly of organisations, coalitions and individuals engaged in risk communication, each with different communication cultures, different interests and abilities to articulate and
participate (Gray et al. 1994). Since the process of information exchange requires a common system of symbols, signs and language, communication will depend on age, sometimes gender, education, current subject knowledge, cultural norms, language, experience and prejudice and bias - on all sides of the communication process.

The exclusion of the lay public from informed decision making under uncertainty by the exclusive usage of an incomprehensible language violates at least the “right to know”. As a consequence, information exchange and risk communication often only works with the use of informed translators (mediators). The media as well as the other participators have their own rules and habits that are rarely similar to those doing exposure and uncertainty assessment. Risk communication should support the social and political processes of managing risks in democratic societies. Consumers react to existing uncertainties, lay people make personal decisions over which they exercise individual control (habits, preference and behaviour) and they participate in democratic government processes (Morgan et al. 1992) by which decisions are made about risk issues over which individuals can exercise relatively little control (technology and industrial development, food production, exposure and risk limits). In the context of exposure assessment for specific sites lay people are often better experts for the regional environment (related to exposure), for the specific exposure conditions (scenarios) and the exposure history than educated exposure scientists.

6.2.4 – Requirements for accepted exposure assessment
Clearness and transparency with respect to the choice of models, methods, assumptions, distributions and parameters is one prerequisite for trust and confidence; openness about uncertainties is another. Exposure assessment as applied science should follow the main scientific desiderata: empirical testing,
documentation and reproducibility of results, explicit reporting of uncertainty, peer review and an open debate about underlying theories and models. This way the main attributes for characterising uncertainty discussed in the last chapter, the appraisal of the knowledge base and the subjectivity of choices are clarified.

Even if adequate documentation exists, a complete and thorough peer review of exposure models can be an extremely time consuming and difficult business. Model assessment should include a re-analysis of all input data, assumptions and model, as well as an examination of all simplifications, formulas, computer code, programming features together with additional runs of the model to examine sensitivities and hidden bugs (GAO 1979). Exposure models as complex models are implemented in special programming languages or spread sheets. Problems in reviewing exposure models might arise from the code testing alone (Henrion 2004, Panko 1998).

It is unrealistic to expect a reviewer to be able to perform a complete assessment, unpaid and single handed. In the case of large models, a proper external assessment will require a multidisciplinary team, and a significant budget” (Morgan and Henrion 1990, p. 20).

Point and range estimates as well as probabilistic models (Monte Carlo simulation) must show complete reproducibility per programming environment since the underlying algorithms are deterministic. They should show asymptotic equivalence of results over different software environments and simulation techniques.

**Recommendation 7:**

Uncertainty analyses for exposure assessment should be documented fully and systematically in a transparent manner, including: quantitative aspects pertaining to data, methods, inputs, models, outputs; sensitivity analysis; qualitative aspects; and interpretation of results.

### 6.3 – Proposals for the presentation/visualisation of uncertainty

The presentation of results should support an unbiased understanding of the results of the exposure assessment to enable the members of the target groups to make informed and independent decisions. This requires a basic understanding of the exposure process (the model from source to dose/burden) and at least an intuitive competence to understand the quantitative data and results in nature and magnitude. The selected scenario, data, model assumptions, results and inherent uncertainties should be communicated in an understandable and scientifically accepted presentation format. Presentations should be tailored to address the questions and information needs of the different audiences. To handle the different levels of sophistication and detail needed, it may be useful to design a presentation in a tiered format where the level of detail increases with each successive tier (U.S. EPA 1997).
**Recommendation 8:**

The results of the assessment should be subject to an evaluation process that may include peer review, model comparison, quality assurance, or comparison to relevant data or independent observations.

6.3.1 – Presentation of numerical results

Textual descriptions of the exposure assessment results might be useful if statements about the mean, the central tendency estimate (median) or a selected quantile of the exposure distribution are given without a description of uncertainty. But each of the point estimates mentioned will have a different level of uncertainty with respect to model assumptions, database and calculation method. A typical wording to describe results might be

- Taking into account the restrictions/the uncertainty/the lack of sufficient data/
- we assume/expect/calculate/ ….  
- that the exposure of the population/of the most exposed group/the highest exposed individual/…
  - is in the range from …. to …. (for x%)
  - is lower than …. for 95%/99%/… of the population  
  - is lower than …. with …. confidence

A textual presentation of results should in no way lead to a mixture of verbal descriptions of numerical results with an evaluation of results. In 2000, the European Commission gave this clear advice:

“... the Scientific Committees should be aware that adjectives such as minimal, negligible, etc. and expressions as ‘no risk’, ‘acceptable risk’, etc. may sound to have a different meaning for scientists, experts and the layman. The glossary could explain the exact meaning attributed to these expressions or, alternatively, each opinion should explain the exact context in which such expressions are used. In general, judgements about ‘acceptability’ ought to be used only when clear legislative terms of reference are available ... otherwise the criterion of acceptability should be explained in detail. In every case, it seems to be very important that the reader is informed about existence or non-existence of official EU legislation of reference within the frame of which the risk assessment judgement is formulated” (EC, 2000, p.174).

Although the advice is given mainly for the description of risk assessment results, it holds completely for exposure assessment, since the quantitative input for risk assessment is exposure assessment and uncertainty analysis. Since any description of the resulting exposure distribution(s) in terms like “very low, low, fair, moderate, high, extreme” includes an evaluation, it must be defined and justified (EnHealth 2002). Comparative reporting schemes like “the majority/90%/95% of data/individuals are lower than the limit/reference/comparison value of ... the (institution)” are incomplete if the limit/reference/comparison values are not reported together with an adequate data description. Comparative evaluation of results without reporting the results
of the assessment will not support the credibility of the reported results. In
general, it will be difficult to give a simple textual description of the expected
variability in exposure results together with a description of the influence of
uncertainty in a mainly textual format (Budescu and Wallsten 1995).

The presentation of results in graphical formats is “state of the art” (U.S. EPA
2000). Although we do not have uniformly accepted recommendations for the
presentation formats, the targets of the visualisation approaches seem to be in
accordance the the following criteria to describe the expected variability in the
target population:

- description of the full range of the exposure distribution by displaying a
cumulative and a density function of the distribution,
- control for the cumulative probability distribution (percent under/over a
given value of),
- description of the central tendency (mean and median=50%-quantile)
and
- description of selected percentage values (1%-,5% and/or 95%-, 99%-quantiles) for which the population exposure is under/over the given quantiles.

Alternative approaches using box and whisker plots, pie charts and different
types of visualisations of density functions are discussed in Ibrekk and Morgan
(1987) and Morgan and Henrion (1990). Each has advantages for specific tasks,
but the performance of a display depends upon the information that a subject is
trying to extract (central tendency or variation).

The visualisation of uncertainty within the graphical presentation formats
introduces an additional dimension in the display. In the simplest form this is
displayed by a set of corresponding confidence intervals or gray/color shadings
around the central tendency estimate function(s). We discuss this in the
following section. In a former project of one of the authors, substantial
interaction with end-users (mostly risk assessors) suggests that it is helpful to
get the audience accustomed to one type of graph first before exposing them to
the many possible variations; cumulative distributions seem to be a good first
choice (especially when you want to show confidence intervals around the
distribution - this does not work well with pdfs). If the audience will accept two
types of graph, cumulative distributions are good for quantities where the
interest is in small values (e.g., toxicity) and inverse cumulative distributions
(exceedance plots) are better where you are interested in high values (e.g.,
exposure, frequency of impacts). A display of the density function adds
information about the shape and the modal values of the distribution (Figure
6.6).

6.3.2 – Communication of quantitative uncertainties
Communicating uncertainty adds complexity because it involves communicating
ranges or distributions of possible risks, rather than single estimates. However,
research studies indicate that the majority of people do understand the
difference between interval and point estimates of risk (Johnson and Slovic
Among those respondents who understood the concept, reporting of uncertainty had mixed effects (Johnson 2003). On one hand, discussion of uncertainty appeared to signal more honesty. On the other hand, discussion of uncertainty led to lower competence ratings of the institutions responsible for risk assessment. Graphical presentation of uncertainty produced higher comprehensibility ratings, but lower trustworthiness ratings. The potential for such responses needs to be considered by scientists and risk managers when deciding how to communicate with consumers. However, the main focus in this section is on finding effective ways for scientists to communicate uncertainty to risk managers.

Routine assessments account for uncertainty by using standard factors and assumptions. In these cases, it is sufficient to give the result, state that the standard factors were applied, and refer the reader to other sources (e.g., an official guidance document) for the derivation and justification of those factors. If there could be questions about the applicability of the standard factors to the case in hand (e.g., for a novel contaminant) then the decision to use them should be justified.

Uncertainties assessed at Tier 1 (qualitative) may be communicated by listing or tabulating them, together with an indication of their direction and magnitude. Possible formats for this are illustrated in chapter 5. In addition, it will generally be desirable to give a more detailed textual discussion of the more important uncertainties in the list, and of their combined effect on the assessment outcome.

Uncertainties assessed at Tier 2 (deterministic) generate alternative point estimates for exposure, and may be communicated in various ways depending on the particular methods used for sensitivity analysis. As a minimum, this should identify which sources of uncertainty have been treated at Tier 2, state and justify the alternative quantitative estimates used for each one (e.g., minimum, maximum and most likely values), present exposure estimates for those combinations of alternative estimates that are considered plausible and state and justify any combinations of estimates that are considered implausible. In addition, it will be useful (especially if upper estimates exceed levels of concern) to show which of the quantified uncertainties have most influence on the outcome.

Uncertainties assessed at Tier 3 (probabilistic) assessments produce probability distributions as outputs. Probability distributions can be communicated in many ways, including:

- Probability density function, showing the relative probability of different values,
- Cumulative distribution, showing the probability of values below any given level,
- Exceedance (inverse cumulative) distribution, showing the probability of values above any given level,
- Summary statistics, e.g., mean or median estimates for the 97.5th percentile exposure together with one or more confidence intervals
Examples of the three types of graphical representation are shown in Figure 6.6. These hypothetical examples show uncertainty distributions for the exposure of the 97.5th percentile consumer; this could equally be done for other percentiles or for the average consumer.

**Figure 6.6.** Examples of 3 different formats for presenting probability distributions.

A more complex graphical format can be used to show a distribution for variability of exposure across the whole population, together with confidence intervals to show uncertainty (e.g., Figure 6.7). This can be used to read off confidence intervals for the exposure of any given percentile consumer.

**Figure 6.7.** Example of cumulative distribution for variability of exposure between consumers (thick curve), with 95% confidence intervals (thin curves) showing uncertainty for each percentile consumer. Other confidence intervals (e.g., 90 or 99%) could be shown, depending on the level of confidence wanted by risk managers.

Cumulative distributions have been found to be more intuitive for non-technical audiences than other kinds of display (Morgan and Henrion 1990), and are convenient for reading off different percentiles (e.g., median, 95th percentile). Cumulative distributions are especially useful when interest is focussed on low
values (e.g., intake of nutrients), while exceedance distributions may be more intuitive when the interest is in high values (e.g., exposure to contaminants). However, the most likely value (mode) and shape of the distribution are shown more clearly by a probability density function, and the U.S. Environmental Protection Agency (1997) recommends showing both cumulative distributions and probability density functions side-by-side. Whatever methods are used for presenting the results, it is helpful to provide a textual explanation as well.

It is essential to provide decision-makers with an assessment of the overall degree of uncertainty in the assessment outcome. Therefore, if the uncertainties for an assessment have been analysed at different tiers (qualitatively, deterministically and probabilistically), it is necessary to find a way of presenting the results together and arriving at an overall characterisation of exposure. This is difficult and subjective but unavoidable, since it is never possible to quantify all uncertainties objectively. Few assessments have attempted to do this in a systematic way, and it would be premature to give firm recommendations. However, a combined presentation should include:

- A list of the uncertainties that have been treated probabilistically (Tier 3), and appropriate graphical, numerical and textual presentation of the results.
- A list of the uncertainties treated deterministically (Tier 2), showing the results obtained with alternative assumptions.
- A list of the uncertainties treated qualitatively (Tier 1), together with an evaluation of the direction and magnitude of their impact on the assessment outcome.

In addition, it will generally be desirable to produce a concise textual and numerical summary of the results, e.g. for use in the executive summary of an exposure assessment. The appropriate format for this will vary from case to case, but one possible format for a Tier 3 assessment might be:

“The median estimate of the 97.5th percentile exposure is x, but this is affected by a number of uncertainties. Uncertainties A, B, C… were analysed probabilistically, resulting in a p% confidence interval of y – z. This included reasonable worst-case assumptions for uncertainties D, E, F…, which were not treated probabilistically. Evaluation of further, unquantified uncertainties suggests that the true 97.5th percentile exposure could be higher/is unlikely to be higher, because…”

Note that the choice of confidence intervals (p%) to use in such statements should be agreed with decision-makers, since it implies a risk management judgement about how much certainty is required. Although 95% intervals are frequently used in biological research, a higher or lower degree of certainty may be appropriate for risk management, and may vary from case to case depending on the other risks and benefits at stake.

In addition to communicating results, it is essential to communicate sufficient information about the methods used so that peer reviewers can fully evaluate them, and so that other specialists could repeat the assessment if desired. This is especially important for sensitivity analysis and probabilistic approaches,
although it may be sufficient to describe them in outline if the reader can be referred to other sources for detail.

6.3.3 – Communication about unquantified uncertainties

A key part is how to communicate the *unquantified uncertainties*. It is often suggested that it is good practice to list or describe the uncertainties affecting an exposure or risk assessment. Cooke (1991, p.3) uses the fourfold distinction for the degree of scientific based reasoning used in the risk communication process between “conjecture – belief - correct reasoning – knowledge”. Many scientific and public heated debates about exposure and risk assessment deal with the status of arguments of the communication partners in this line. However, simply listing and categorising uncertainty is not very helpful to the decision-maker. Section 5.1.4 gives an overview on how to assess the sources of uncertainty.

What the decision-maker needs to know is the combined effect of the uncertainties on the assessment outcome; in other words, how different the true exposure might be. Therefore it is desirable, even in a qualitative assessment, to give some indication of the direction and magnitude of each individual source of uncertainty and the combined effect of all the uncertainties considered.

One promising attempt to do this might be to present a table listing the unquantified uncertainties and indicating the direction and magnitude of each to indicate relative magnitude and direction of influence on risk estimate (see Table 12.2 for example). In a second step an overall assessment of the combined influence of the tabulated uncertainties on the risk estimate might be presented. Of course, all this represents a subjective and qualitative statement, but it has the character of a transparent visualisation of an evaluation, based on the knowledge and experience of the exposure and risk expert (group). We think it will work best when the magnitudes can be expressed in relation to some decision threshold, e.g. an uncertainty which might take the risk above the acceptable limit (set by risk managers) could be indicated as highly relevant. Although the approach seems to be quite simple, it might give a framework for an qualitative evaluation of the content, steps and results as a basis for a transparent discussion.

Two aspects of magnitude are worth considering. One is the relative magnitude of different sources of uncertainty, which can help to prioritise which uncertainties to reduce by collecting additional data. The other is the magnitude of the uncertainties compared to the margin between the estimated exposure and any level of concern to the risk manager (if known). This is important when considering whether the uncertainties are large enough to change the overall outcome and risk management judgement.

Clearly, any qualitative assessment of the direction and magnitude of uncertainties and of their combined influence on the assessment outcome is bound to be subjective. This makes it very dependent on the knowledge, experience and expertise of the assessor. Some might argue that this makes it inappropriate or even dangerous to do. However, the alternatives are even less attractive: leave the assessment of uncertainty to risk managers (who generally have less relevant knowledge, experience and expertise), or ignore uncertainty...
altogether (in which case public decisions are based on best estimates without
attention to the likelihood or consequences of other outcomes). Quantification
may help but is not possible for all uncertainties. Therefore the least worse
option is to start with a qualitative assessment, interpret it cautiously to take
account of its subjectivity and use it to decide whether a more quantitative
assessment is needed (see section 5.1.4.4). A simple approach for this could
comprise the following elements: (a) consider all parts of the model and list all
identifiable sources of uncertainty, (b) subjectively evaluate any directional
influence of each source of uncertainty, (c) evaluate the magnitude of each
source of uncertainty on the assessment outcome, ideally relative to the relevant
risk management threshold, (d) evaluate the combined influence of the listed
uncertainties on the assessment outcome (direction and magnitude) and (e)
finally, if the combined influence of the uncertainties is clearly not sufficient to
alter the risk management judgement, then further assessment may not be
required. If, on the other hand, the combined influence indicates a sufficient
probability that the risk management judgement could be altered, then a more
refined assessment may be justified.

**Recommendation 9:**

Where appropriate to an assessment objective, exposure assessments should be
iteratively refined over time to incorporate new data, information, and methods
in order to reduce uncertainty and improve the characterization of variability.

The subjectivity of the qualitative assessment (see section 5.1.4.3) also opens
the possibility of conscious or unconscious bias by the assessor. For this reason,
it is desirable to report the steps from (a) to (f) in a transparent way so that
others can review and evaluate the judgements that have been made.

This has the advantage that it is always possible to do and that it is sufficient if
the result is clearly conservative (protective) overall. But it has disadvantages
with regard to subjectivity when the outcome is not clearly conservative and
when using separate uncertainty factors for many parameters that can lead to
compounding conservatism. If an exposure and risk assessment contains a
number of conservative assumptions, then the above table is likely to end up
with an overall assessment that the true risk is probably lower than the
quantitative estimate. However, if your assessment attempts to use realistic
estimates/distributions for most inputs, then you are likely to end up with a table
of unquantified uncertainties. This undoubtedly is a difficulty for decision-
makers unless the assessor can evaluate the combined uncertainty relative to
the decision-makers' decision threshold.

As a conclusion of this section about the role of uncertainty analysis and
description, it is worth noting that despite all the work and effort, a scientifically
adequate analysis and description of uncertainty will lead to some discomfort
and might introduce an element of communication conflict. This is a
consequence of the state of uncertainty and should be considered. Some people
are tempted not to show the quantified and especially the unquantified
uncertainties, but that does not solve the underlying problem. Since

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transparency is an important attribute of openness and trust, both will contribute to confidence into those involved in dealing with risks.

6.4 – Avoiding typical conflicts in risk communication

A high degree of communication between those involved in the process is a necessary but sometimes not sufficient prerequisite to avoid risk communication conflicts. Those persons who represent organisations in the communication process and especially in the public should obtain at least some basic understanding of the benefits and problems of exposure, uncertainty and risk assessment. But this can not be expected for all communication partners. If different organisations and groups with a different background of interests, faculty and profession are involved, it might be useful to plan the risk communication process. At least some types of conflicts mentioned below can be anticipated, avoided or reduced.

Information sharing: Whether organisations or facilities disclose or withhold any relevant information or specific data needed for the specification and calculation of an exposure scenario, distrust and public conflict will be guaranteed. Uncertainty is seldom, if ever, an acceptable excuse for waiting to communicate or deliver risk information (Covello et al. 1988). The “right to know” all relevant information, the exposure results, the uncertainties and the risk evaluations is an important issue for organisations as well as for the public.

Participation: Non-involvement in the risk communication process of those individuals, organisations and institutions who have an organisational, professional or individual interest in the risk topic might lead to distrust, multiple assessments and later to a divergence of results and evaluations. The key actors should at least be informed and, depending on the public character of the process, be invited to share the process. A lack of involvement might and often will result in conflicts/misunderstandings about the completeness or correctness of data, the methods and the appropriateness of the standards and norms used in risk evaluation.

Facts and methods: Obtaining agreement in the scientific community about the selected exposure scenario, the assumptions, the models, the data, the methods and the remaining uncertainties should be an early target of any exposure assessment. Seeking consensus about the selected (sub-)population, the quality of input and the model will enhance the acceptance of the results. Involving different scientific approaches and describing the existing level of uncertainty increases the quality of the assessment and might lead to an anticipation of the pro and con arguments coming in a later stage of the risk communication process. But if the data and results are highly uncertain, some people are likely to complain that the given facts are too uncertain to trust.

Evaluation of results: The result of an exposure assessment is a value or a distribution of expected exposure values, together with a range of uncertainty. If limiting values with some formal or accepted legitimization exist (laws, directives, parliamentary governmental or organisational decisions), then the evaluation of the results is not in the hands and responsibility of the risk.
management. If the evaluation of the results is carried out for new substances (hazards), the choice of the level of safety is a matter of scientific and public debate. In the second case answers to questions like “What is safe enough?” or “What are the safety targets?” must be found. It is the right of any individual or group to make a claim for “No exposure! No risk!”. Acceptability for a burden of exposure, for uncertainty and for risks cannot be demanded by comparison to other individual risks or by cross-reference to legislation for other hazards. The evaluation of an exposure and uncertainty assessment as well as the risk regulation must follow the laws and the rules of a democratic society. But even if a justified regulation is notified, it is the right of each individual communication partner not to accept it.

Consequences and necessary actions: Since it seems to be difficult to find public consensus in the evaluation of exposure assessment results, it should be expected to be more difficult to find an agreement about the necessity and the kind of actions as a consequence of the assessment results, including the uncertainty. Covello et al. (1988) state that, “Often, actions are what people most want to know about. … People want to know what you doing to reduce emissions, not just how much is emitted and how many deaths or illnesses may result”. In risk communication the choice of no or adequate actions will be questioned by different groups for different targets, and uncertainty (“Will you wait until … has happened?”) might be an important argument in the demand for action.

The guiding risk communication tips of the Center of Disease Control and Prevention (Reynolds 2002) “Don’t give overassurance!”, “Acknowledge uncertainty!” and “Explain the process to find the answer!” might help sometimes to communicate uncertainty in an understandable and fair manner. Levinson (1991) advises that companies as well as organisations in general can not improve the relationships to communication partners by risk communication alone: “The most productive way is to build trust”, which might be done by exposure and risk reduction programs (reduction of the use of toxic substances, of emission and of hazardous waste). Organisation should develop a risk communication culture that supports this process.

**Recommendation 10:**

Communication of the results of exposure assessment uncertainties to the different stakeholders should reflect the different needs of the audience in a transparent and understandable manner.

### 6.5 - Conclusions

As in everyday life, the credibility of the players in risk communication (individuals or organisations) has a central role in risk communication. Credibility is a basic element of risk communication with respect to scientific correctness and transparency about the current limitations in knowledge and existing uncertainty. Social trust is the main factor in risk acceptance and risk management (Renn and Levine 1991). Credibility of organisations, institutions
and individuals can be destroyed very quickly and very efficiently (Alhakami and Slovic 1994) and credibility develops very slowly (Bord and O’Connor 1992). These three statements might explain some aspects of the profile and the credibility crisis that many institutions and organisations are actually dealing with. A change in dealing with uncertainty in exposure assessment as well as a change in communicating about it might improve the actual situation.

7 – Recommendations

This IPCS monograph has identified ten guiding principles, as recommendations for uncertainty analysis. The principles are mentioned, where most appropriate, in the chapters of this monograph.

Guiding principles are considered to be the general desirable goals or properties of good exposure assessment. These are general principles, and are supported in the text by more detailed recommendations for good practice.

1. Uncertainty analysis should be an integral part of exposure assessment.

2. The objective and level of detail of the uncertainty analysis should be based on a tiered approach and be consistent with the overall scope and purpose of the exposure and risk assessment. The amount of effort and detail should be consistent with the objective. All parts of the uncertainty characterization should be conducted in conformity with the specified objective and level of detail. Ideally, when exposure assessment is conducted as part of a risk assessment, uncertainty in exposure assessment should be characterized in such a way that it contributes to an overall characterization of uncertainty in risk.

3. Sources of uncertainty and variability should be systematically identified and evaluated in the exposure assessment. It is not possible to quantify all sources of uncertainties. Therefore, expression of uncertainty, variability, or both in exposure estimates may be qualitative or quantitative, but should be quantified to the extent that is scientifically achievable. The concepts of variability and uncertainty are distinct and typically there will be a need to distinguish these based upon the problem formulation.

4. The presence or absence of moderate to strong dependencies between inputs is to be discussed and appropriately accounted for in the analysis.

5. Data, expert judgment, or both should be used to inform the specification of uncertainties for scenarios, models, and inputs.

6. Sensitivity analysis should be an integral component of the assessment. The results of sensitivity analysis should be used iteratively as part of the exposure variability and uncertainty assessment to help prioritize the development of quantitative estimates of variability, uncertainty, or both. The results of sensitivity analysis should be used to provide
insight on the importance of different sources of variability, uncertainty, pathways and other factors of importance to the assessment.

7. Uncertainty analyses for exposure assessment should be fully and systematically documented in a transparent manner, including: quantitative aspects pertaining to data, methods, inputs, models, outputs; sensitivity analysis; qualitative aspects; and interpretation of results.

8. The results of the exposure assessment including the uncertainty should be subject to an evaluation process that may include peer review, model comparison, quality assurance, or comparison to relevant data or independent observations.

9. Where appropriate to an assessment objective, exposure assessments should be iteratively refined over time to incorporate new data, information and methods in order to reduce uncertainty and improve the characterization of variability.

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

8 – Conclusions

This IPCS monograph describes, characterizes and provides guidance for uncertainty analysis in routine exposure assessment work. It also discusses challenges and limitations, as it cannot answer all the questions which may be posed in uncertainty analysis; rather, it demonstrates that uncertainty analysis is a dynamic process.

An uncertainty analysis gives the assessor the opportunity to re-evaluate the scenario, model approaches and parameters of the analysis, and to consider their influence in the overall analysis. The practical impact of uncertainty analysis is illustrated within the chapters on case studies, which also clarify how uncertainty analyses follow a systematic methodology, based on a tiered approach, and consider all possible sources of uncertainty. The first step in uncertainty analysis consists in a screening, followed by a qualitative analysis, and two levels of quantitative analysis, taking deterministic and probabilistic data. The assessor should be aware that an uncertainty analysis cannot answer all the questions which, moreover, may lead to new questions.

Finally, the results of the uncertainty analysis should be adequately communicated together with the results of the assessment. Addressing the uncertainties of the exposure assessment enables the risk assessor to distinguish risk characterization and risk assessment. Further, the results of the exposure assessment enable the risk manager to identify the key factors which influence exposures and risks.
Chapter 1

Chapter 2
[Methodical aspects of probabilistic modelling]”, Umweltwissenschaften und Schadstoff-
Forschung - Zeitschrift für Umweltchemie und Ökotoxikologie 11(5):292-298

WHO (2004): “IPCS Glossary of Key Exposure Assessment Terminology” Part 2 of the
“IPCS Risk Assessment Terminology”, IPCS Harmonization Project Document No. 1,
available at http://www.who.int/ipcs/methods/harmonization/areas/ipcsterminologyparts1and2.pdf

Chapter 3
Lebensmittel- und Nährstoffaufnahme in der Bundesrepublik Deutschland”,
Wissenschaftlicher Fachbuchverlag Dr. Fleck, Niederkleen, Vol XI, Verbundstudie
Ernährungserhebung Risikofaktoren Analytik (VERA) Schriftenreihe

BgVV - Federal Institute for Health Protection of Consumers and Veterinary Medicine
(2001): "Workshop on Exposure of Children to Substances used as Ingredients in
Pesticides", Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmizin,
German Federal Ministry for the Environment, Nature Conservation and Nuclear Safety,
Grant No. 201 61 218/01, Berlin, September 27-29, available at

Monitoring“, Bundesamt für Verbraucherschutz und Lebensmelsicherheit, available at
http://www.bvl.bund.de/cln_007/DE/01__Lebensmittel/01__Sicherheit__Kontrollen/03__Monitoring/Monitoring__node.html__nnn=true

factors Influencing children's exposure, and the data available to characterize and assess
that exposure”, Environ. Health Perspect., 108(6), 475-486

Emond, M.J.; Lanphear, B.P.; Watts, A.; Eberly, S. and Members of the Rochester Lead-in-
Relationship between Dust Lead and Children's Blood Lead”, Environmental Research,
72(1):82-92

Regulation (EC) No 1488/94 on Risk Assessment for existing substances and Directive 98/8/EC of
the European Parliament and of the Council concerning the placing of biocidal products on the market”, Part I,
European Chemicals Bureau, Institute for Health and Consumer Protection, Joint Research
Centre, European Commission, EUR 20418 EN/1

Guidance on Exposure Estimation”, DG Environment, B4-3040/2000/291079/MAR/E2, June,

Fiserova-Bergerova, V., Pierce, J.T. and Droz, P.O. (1990): “Dermal absorption Potential of


DRAFT FOR PUBLIC REVIEW: DO NOT CITE OR QUOTE


Reynolds, B., ed. (2002): “Crisis and Emergency Risk Communication”, Centers for Disease Control and Prevention (CDC) and Agency for Toxic Substances and Disease Registry, Atlanta, USA, October


Means for Assessment of Risks to Public Health, Commission on Life Sciences, National Academy Press, Washington, D.C.


Tarkowski, S. (1986): “Environmental Health in Europe – the WHO Perspective”, invited reading at the 2nd Nordic Symposium “Trace Elements in Human Health and Disease”, Odense, Denmark, August


Chapter 11


Chapter 12

10 – Annex I: Glossary of terms for human exposure assessment

The below terms have been adopted or adapted from existing definitions for use in the context of human exposure assessment.

**Accuracy**
Degree of agreement between average predictions of a model or the average of measurements and the true value of the quantity being predicted or measured. Accuracy is also a criteria used to evaluate the knowledge base uncertainty. It focuses on the identification of the most important bottlenecks in the available knowledge and the determination of its impact on the quality of the result.

**Aleatory uncertainty**
Aleatory is of or pertaining to natural or accidental causes and cannot be explained with mechanistic theory. Generally interpreted to be the same as stochastic variability.

**Appraisal of the knowledge base**
A characteristic of the uncertainty. It is used for qualitative characterization of the source of uncertainty. The appraisal of the knowledge base focuses on the adequacy of the available knowledge base for the exposure assessment (e.g., identification of data gaps and their impact on outcome).

**Bias**
also referred to as systematic error. Difference between the mean of a model prediction or of a set of measurements and the true value of the quantity being predicted or measured.

**Bootstrap simulation**
A statistical technique based on multiple re-sampling with replacement of the sample values or re-sampling of estimated distributions of the sample values that is used to calculated confidence limits or perform statistical tests for complex situations or where the distribution of an estimate or test statistic cannot be assumed.

**Choice space**
Choice space is a criterion used to evaluate the subjectivity of choices characteristic of uncertainty. It focuses on spanning the alternative choices.

**Confidence Interval**
An estimated two-sided interval from the lower to upper confidence limit of an estimate of a statistical parameter. This interval is expected to enclose the true value of the parameter with a specified confidence. For example, 95 percent confidence intervals are expected to enclose the true values of estimated parameters with a frequency of 95 percent.

**Controllable Variability**
Sources of heterogeneity of values of time, space, or different members of a population that can modified in principle at least in part by intervention, such as a control strategy. For example, variability in emissions of a chemical to the atmosphere could be modified via a control strategy. For both population and individual risk, controllable variability is a component of overall variability.

**Credibility Interval**
Similar to a confidence interval, except that a credibility interval represents the degree of belief regarding the true value of a statistical parameter.

**Data Quality Objective**
Expectations or goals regarding the precision and accuracy of measurements, inferences from data regarding distributions for inputs, and predictions of the model.
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Exposure Route
The way in which an agent enters a target after contact (e.g., by ingestion, inhalation, or dermal absorption).

Goodness-of-Fit Test
A procedure for critiquing and evaluating the potential inadequacies of a probability distribution model with respect to its fitness to represent a particular set of observations.

Influence of choices on results
Influence of choices on results is a criterion used to evaluate the subjectivity of choices characteristic of uncertainty. It determines the influence of the choices on the results.

Influence of situational limitations on choices
Influence of situational limitations on choices is a criterion used to evaluate the subjectivity of choices characteristic of uncertainty. It determines the influence of situational limitations (e.g., money, tools and time) on the choices.

Inherent Randomness
Random perturbations that are irreducible in principle, such as Heisenberg’s Uncertainty Principle.

Inputs
Quantities that are input to a model.

Inter-individual Variability
see Variability

Intra-individual Variability
see Variability

Intersubjectivity among peers and among stakeholders
Intersubjectivity among peers and among stakeholders is a criterion used to evaluate the subjectivity of choices characteristic of uncertainty. It focuses on both the similarity and controversy of choices among peers and among stakeholders.

Level of Uncertainty
A characteristic of the uncertainty. It is used for qualitative characterization of the source of uncertainty. The level of uncertainty is essentially an expression of the degree of severity of the uncertainty, as seen from the assessors’ perspective.

Model
A set of constraints restricting the possible joint values of several quantities. A hypothesis or system of belief regarding how a system works or responds to changes in its inputs. The purpose of a model is to represent as accurately and precisely as necessary with respect to particular decision objectives a particular system of interest.

Model Boundaries
Designated areas of competence of the model, including time, space, pathogens, pathways, exposed populations, and acceptable ranges of values for each input and jointly among all inputs for which the model meets data quality objectives.

Model Detail
Level of simplicity or detail associated with the functional relationships assumed in the model compared to the actual but unknown relationships in the system being modeled.
**Model Structure**
A set of assumptions and inference options upon which a model is based, including underlying theory as well as specific functional relationships.

**Model Uncertainty**
Bias or imprecision associated with compromises made or lack of adequate knowledge in specifying the structure and calibration (parameter estimation) of a model.

**Parameter**
A quantity used to calibrate or specify a model, such as ‘parameters’ of a probability model (e.g., mean and standard deviation for a normal distribution). Parameter values are often selected by fitting a model to a calibration data set.

**Plausibility**
Plausibility is a criterion used to evaluate the knowledge base uncertainty. It focuses on the completeness of the knowledge base and the acknowledgement of ignorance when applicable.

**Precision**
A measure of the reproducibility of the predictions of a model or repeated measurements, usually in terms of the standard deviation or other measures of variation among such predictions or measurements.

**Probabilistic analysis**
Analysis in which distributions are assigned to represent variability or uncertainty in quantities. The form of the output of a probabilistic analysis is likewise a distribution.

**Probability**
Defined depending on philosophical perspective. 1. the frequency with which we obtain samples within a specified range or for a specified category (e.g., the probability that an average individual with a particular mean dose will develop an illness); 2. degree of belief regarding the likelihood of a particular range or category.

**Random error**
Processes that are random or statistically independent of each other, such as imperfections in measurement techniques that lead to unexplainable but characterizable variations in repeated measurements of a fixed true value. Some random errors could be reduced by developing improved techniques.

**Refined Method**
This method is intended to provide accurate exposure and risk using appropriately rigorous and scientifically credible methods. The purpose of such methods, models or techniques is to produce an accurate and precise estimate of exposure and/or risk consistent with data quality objectives and/or best practice.

**Reliability**
Reliability is a criterion used to evaluate the knowledge base uncertainty. It focuses on the identification of the scientific status of the knowledge base and the determination of its quality soundness.

**Representativeness**
The property of a sample (set of observations) that they are characteristic of the system from which they are a sample or which they are intended to represent, and thus appropriate to use as the basis for making inferences. A representative sample is one that is free of unacceptably large bias with respect to a particular data quality objective.

**Robustness**
Robustness is a criterion used to evaluate the knowledge base uncertainty. It focuses on the predictability of the values and of the results and on the dependency relationships.
Sampling distribution
A probability distribution for a statistic.

Sensitivity of choices to the analysts’ interests
Sensitivity of choices to the analysts’ interests is a criterion used to evaluate the subjectivity of choices characteristic of uncertainty. It assesses the sensitivity of the choices to the analysts’ interests.

Scientific consistency
Scientific consistency is a criterion used to evaluate the knowledge base uncertainty. It focuses on the maturity of the underlying science and their limitations.

Screening Method
This method is intended to provide conservative over-estimates of exposure and risk using relatively simple and quick calculation methods and with relatively low data input requirements. The purpose of such methods, models or techniques is to eliminate the need for further more detailed modeling for scenarios that do not cause or contribute to high enough levels of exposure and/or risk to be of potential concern. If a screening method indicates that levels of exposure and/or risk are low, then there should be high confidence that actual exposures and/or risk levels are low. Conversely, if a screening method indicates that estimated exposure and/or risk levels are high, then a more refined method should be applied since the screening method is intentionally biased. See Refined Method.

Statistic
A function of a random sample of data (e.g., mean, standard deviation, distribution parameters).

Stochastic uncertainty
also referred to as random error. See definition for random error.

Stochastic Variability
Sources of heterogeneity of values associated members of a population that are a fundamental property of a natural system and that as a practical matter cannot be modified, stratified, or reduced by any intervention. For example, variation in human susceptibility to illness for a given dose for which there is no predictive capability to distinguish the response of a specific individual from that of another. Stochastic variability contributes to overall variability for measures of individual risk and for population risk.

Subjective probability distribution
A probability distribution that represents an individual’s or group’s belief about the range and likelihood of values for a quantity, based upon that person’s or group’s expert judgment.

Subjectivity of choices
A characteristic of the uncertainty, also called value-ladenness of choices. It is used for qualitative characterization of the source of uncertainty. The subjectivity of choices expresses the influence of the choices made during the exposure assessment including the influence of situational limitations (e.g., money and time) on choices, the analysts’ interests and the subjectivity among peers and stakeholders.

Surrogate data
Substitute data or measurements on one quantity used to estimate analogous or corresponding values of another quantity.

Systematic Error
see Bias.

Variability
Heterogeneity of values over time, space, or different members of a population, including stochastic variability and controllable variability. Variability implies real differences among members of that population. For example, different individual persons have different intake and susceptibility. In relation to human exposure assessment, differences over time for a given individual are referred to as intra-individual variability; differences over members of a population at a given time are referred to as inter-individual variability.
11 – Annex II: Case study

11.1 - Introduction
This is an example exposure assessment that illustrates quantitative representations of uncertainty and variability at the higher tiers of an exposure assessment. This case study is based on exposures to a persistent, bioaccumulative, and lipid-soluble compound that humans are exposed to through fish consumption. This compound is fictional and referred to here as PBLx, but it has properties that correspond to known persistent compounds. Specific goals of this case study are to illustrate (a) the types of uncertainty and variability that arise in exposure assessments, (b) qualitative uncertainty assessment, (c) how distributions are established to represent variability and uncertainty, (d) differences among alternate variance propagation methods, (e) how to distinguish uncertainty from variability, and (f) how to communicate the results of an uncertainty analysis.

The overall process of characterizing the exposure scenario along with the magnitude, variability, and uncertainty of a specific exposure includes the following steps:

- description of exposure assessment context and question
- exposure scenario definitions
- proposed exposure model
- parameters and data used
- sensitivity analysis
- output variance propagation, and
- uncertainty importance evaluation

Uncertainty analysis and sensitivity analysis are tools that provide insight on how model predictions are impacted by data precision. One of the issues in uncertainty analysis that must be confronted is how to rank both individual inputs and groups of inputs according to their contribution to overall uncertainty. In particular, there is a need to distinguish between the relative contribution of true uncertainty versus variability (i.e., heterogeneity) as well as distinguishing model uncertainty from parameter uncertainty. This case study illustrates methods of uncertainty representation and variance characterization.

11.2 - Methods used in the case study
The composition of the case study includes a conceptual model, the modeling approach, data available, construction of input distributions, and variance propagation method. When evaluating uncertainty it is important to consider how each of these elements contributes to overall uncertainty.

11.2.1 - Conceptual model: the context, the question, and scenario development
The goal of the conceptual exposure model is to establish exposure links via exposure pathways to exposure routes and relative magnitude of uptake or intake by different exposure routes. Based on the current consensus of the scientific community, exposure is defined in terms of contact with the visible
exterior of the person. These contact points include the skin and the openings into the body, such as mouth and nostrils.

**Figure 11.1. Multimedia, multi-pathway, multi-route exposure assessment**

The conceptual model must address the scenario definition, which includes specification of the pollutant source, environmental transport and transformation, exposure pathways, exposure routes, and the amount of chemical taken up through various routes and attributable to specific pathways and sources. The route of exposure refers to the way that an agent enters the receptor during an exposure event. Exposure routes include the inhalation of gases and aerosols, ingestion of fluids and foods, dermal contact with water or soil, and dermal uptake of chemicals that contact skin surfaces. Because health impacts of an exposure may vary significantly among the routes of contact, the route of potential uptake is considered a very important attribute of an exposure event. An environmental pathway is the course that a chemical or biological agent takes from a source to an exposed individual. This pathway describes a unique mechanism by which an individual or population is exposed to agents originating from a defined location, micro-environment and environmental medium. Exposure scenarios are used to define plausible pathways for human contact.

The general intake model used for the case study is adapted from an Environmental Protection Agency (EPA) model. We use this model in the form adopted for generalized multi-pathway exposure modeling as described in the WHO-IPCS Environmental Health Criteria report 214 “Human Exposure Assessment” (Chapter 6, IPCS, 2000). In this form the model expresses the potential average daily intake or potential daily dose, $ADD_{pot}$ over an averaging time $AT$ as

$$ADD_{pot} = \left[ \frac{C_i}{C_j} \right] \times \left[ \frac{IU_i}{BW} \right] \times \frac{EF \times ED}{AT} \times C_j$$  \hspace{1cm} [1]$$

where $[C_i /C_j]$ is the intermedia transfer function that relates concentration in medium j to concentration in medium i (for example tap water to indoor air); $C_i$ is the contaminant concentration in the exposure media i; $C_j$ is the concentration in environmental media j; $IU_i$ is the intake/uptake factor (per body size [BW]) for exposure media i; $EF$ is the exposure frequency (day/year) for this population, $ED$ is the exposure duration (years), and $AT$ is the averaging time for population exposure (days).
11.2.2 - Modeling approach

In the case study presented below, we apply Equation 1 with the appropriate monitoring data, bioconcentration measurements, and human consumption data to make exposure estimates for the exposed population. The model is used to organize and manage information on:

1. The magnitude of the source medium concentration: that is, the level of contaminant that is measured or estimated at a release point.
2. The contaminant concentration ratio: which defines how much a source-medium concentration changes as a result of dilution, transport, and inter-media transfers before human contact occurs.
3. The level of human contact: which describes (often on a body-weight basis) the frequency (days per year) and magnitude (kg/day) of human contact with a potentially contaminated exposure medium.
4. The duration of potential contact: relates to the fraction of lifetime, for the population of interest, during which an individual is potentially exposed.
5. The averaging time: the appropriate averaging time is based on the type of health effects under consideration. The averaging time can be the lifetime (as is typical for cancer as an endpoint), the exposure duration (as is typical for long-term chronic but non-cancer endpoints) or some relatively short time-period (as is the case for acute effects).

11.2.3 - Constructing input distributions

The value of information derived from a parameter uncertainty analysis is very much dependent on the care given to the process of constructing the input parameter distributions. One begins the process of constructing a distribution function for a given parameter by assembling values from the literature, from a sampling program, from experiments, and/or from expert knowledge. These values should be consistent with the model and its particular application. The values will vary as a result of measurement error, spatial and temporal variability, extrapolation of data from one situation to another, lack of knowledge, etc. The processes of constructing a distribution from limited and imprecise data can be highly subjective. Because the uncertainty analyst must often apply judgment to this process, there is a need for expertise and wisdom. This process becomes more objective as the amount of data for a given parameter increases. However, a large set of data does not necessarily imply the existence of a suitable distribution function.

When constructing input distributions for an uncertainty analysis, it is often useful to present the range of values in terms of a standard probability distribution. It is important that the selected distribution be matched to the range and moments of any available data. In some cases it is appropriate to simply use the raw data or a custom distribution. Other more commonly used standard probability distributions include the normal distribution, the lognormal distribution, the uniform distribution, the log-uniform distribution, and the triangular distribution. For the case study presented below, we use lognormal distributions.
For any case study built around Equation 1, we have to consider for model input parameters that provide emissions or environmental concentrations, intermediate transfer factors, ingestion (or other intake) rates, body weight, exposure frequency, and exposure duration. For our specific case study below, we are interested in concentrations in surface waters due to deposition from the atmosphere. The relevant intermediate transfer factor is the bioconcentration factor for fish concentration from surface water concentrations. The intake data we need is the magnitude and range of fish ingestion in our exposed population. Because PBLx is a persistent compound that accumulates in fat tissues, we will not focus for this case on exposure frequency and duration but on long-term average daily consumption.

11.2.4 - Variance propagation methods
To carry out the case studies requires the selection of analytical and statistical simulation methods to propagate the parameter variance through to output variance. The methods considered here include analytical variance propagation, factorial design, discrete probability distribution arithmetic (DPD), unmodified Monte Carlo (MC) sampling, and a modified Monte Carlo sampling method referred to as Latin Hypercube Sampling (LHS). We illustrate the relative advantages and limitations of these variance propagation methods in our case study.

For many mathematical operations, including addition, subtraction, multiplication, division, logarithms, exponentials, power relations, etc. there are exact analytical expressions for explicitly propagating input variance and covariance to model predictions of output variance (Bevington, 1969). In analytical variance propagation methods, the mean, variance, and covariance matrix of the input distributions are used to determine the mean and variance of the outcome. The following is an example of the exact analytical variance propagation approach. If \( w \) is the product of \( x \) times \( y \) times \( z \), then the equation for the mean or expected value of \( w \), \( E(w) \), is:

\[
E(w) = E(x) \times E(y) \times E(z) \tag{2}
\]

The variance in \( w \) (the standard deviation squared) is given by:

\[
\sigma_w^2 = \left[ E(w) \right]^2 \left[ \frac{\sigma_x^2}{[E(x)]^2} + \frac{\sigma_y^2}{[E(y)]^2} + \frac{\sigma_z^2}{[E(z)]^2} + \frac{2\sigma_{xy}}{[E(x)E(y)]} + \frac{2\sigma_{xz}}{[E(x)E(z)]} + \frac{2\sigma_{yz}}{[E(y)E(z)]} \right] \tag{3}
\]

where \( \sigma_x^2, \sigma_y^2, \) etc. are the variances in \( x, y, \) etc. and \( \sigma_{xy}, \sigma_{xz}, \) etc., are the covariance of \( x \) and \( y, \) etc. The covariance of the population is defined as:

\[
\sum_{i=1}^{n} [(x_i - \bar{x})(y_i - \bar{y})] \tag{4}
\]
Bevington (1969) lists variance propagation solutions like the one above for several mathematical operations.

In a factorial design, we represent each model input by a small number (n) of values that characterize the range of the inputs. It is typical that n is 2 (High, Low) or 3 (High, Medium, Low) and the estimates of high and low represent a range pre-defined by confidence limits. If there are m model inputs, then a factorial design requires $n^m$ calculations of an outcome. For example, a model with three inputs represented by three levels (High, Medium, Low) has 27 outcomes—HHH, HHM, HMH, HMM, MHH, MHM, MMM, . . . LLL. In this case, the outcome variance can be estimated from the variance in the 27 predicted outcomes. Correlation effects cannot be characterized using simple factorial design.

DPD arithmetic is a method for replacing continuous distributions with simple discrete distributions that approximate the confidence intervals and the moments (e.g., mean and variance) of the distribution being approximated. The penalty for this simplification is some loss of information about the shape of the inputs and the sources of variance. In a DPD approach, the “high” value is selected to represent the mean of a specified segment (e.g. upper 33 %) of a distribution. This condenses the number of discrete values used to represent each factorial combination. Operationally, the DPD approach works like the factorial design. The major difference is in the level of effort used to select a small set of values to represent an input distribution. In the factorial design, a high value represents an upper bound of the distribution, the middle value, the center, etc. In addition, DPD differs from the factorial method by allowing, with some effort, inclusion of some correlations among the inputs (Morgan and Henrion, 1990).

In an unmodified Monte Carlo method, simple random sampling is used to select each member of the m-tuple set. Each of the input parameters for a model is represented by a probability-density function that defines both the range of values that the input parameters can have and the probability that the parameters are within any subinterval of that range. In order to carry out a Monte Carlo sampling analysis, each input is represented by a cumulative distribution function (CDF) in which there is a one-to-one correspondence between a probability and values. A random number generator is used to select probability in the range of 0 to 1. This probability is then used to select a corresponding parameter value.

In contrast to unmodified Monte Carlo sampling, Latin Hypercube Sampling (LHS) uses "stratified" random sampling to select each member of an m-tuple set. Whereas simple random sampling uses chance to evenly select values in the range of an input parameter, LHS places restrictions on possible unevenness (Iman and Shortencarier, 1984). To generate an m-tuple set using LHS, each input distribution is divided into k intervals of equal probability. From these intervals random variables may be selected in two ways. In "normal" LHS, values are chosen randomly from each probability interval. Alternatively, a midpoint method, similar to the discrete and factorial designs, uses the median of each interval as inputs (Morgan and Henrion, 1990). This selection process is
repeated for all the probabilistic inputs. In this way, sample scenario inputs converge more rapidly toward the true outcome moments.

11.3 – Case study: PBLx exposure from fish ingestion
As a specific case study, we constructed information on a chemical designated as PBLx. This compound is persistent both in the ambient environment and in human tissues. It is also bioaccumulative and lipid soluble. PBLx is a dioxin-like compound. However, it should be noted that this example does not reflect WHO recommendations for dioxin exposure assessment. We consider long-term historical releases of PBLx to the atmosphere over large regions with resulting global deposition to both ocean and surface waters. Measurements reveal that concentrations of PBLx in ocean and surface waters are similar. In both ocean and surface waters this compound is transferred to the tissues of fish that are consumed by humans. There are laboratory measurements of PBLx biotransfer factors (BCFs) but these measurements do not provide sufficient information to establish different PBLx BCF values in ocean and surface water. So we must assume that these measurements reflect the BCF that would be observed in either ocean or surface water. We also have information on fish consumption that can be used to assess human contact. Because our water-concentration data and BCF measurements are not specific to either ocean or fresh water systems, we do no attempt to distinguish consumption according to ocean or fresh-water sources.

11.3.1 - Elements of the exposure assessment: context and question
In this case study, the issue of concern is the widely distributed exposure of human populations to PBLx, which is a persistent pollutant with multimedia and multi-pathway exposure potential. For PBLx, exposures occur primarily through food pathways. Here we focus on fish-ingestion exposures from PBLx emissions to air that are deposited on ocean and fresh water, and accumulated in both ocean and freshwater fish. This situation focuses attention on three key pieces of information—concentration in water, biotransfer to fish, and human consumption of fish.

11.3.2 - Scenario definition
PBLx exposure through fish ingestion represents a case in which highly variable and uncertain data must be characterized. The exposure route involves the ingestion of fish contaminated by PBLx and incorporates the variability/uncertainty in water concentrations, a fish bioconcentration factor (BCF) and fish intake to define the variance in the distribution of likely human intake of PBLx.

11.3.3 - Model selection
In order to illustrate the use of the variance propagation methods described above, we have selected as a case study a simple three-input exposure model. The three inputs for this model include water concentration, fish BCF, and fish...
consumption rates. The model output is dose expressed in µg/d averaged over a
one-year exposure period. This model has the form:

\[
\text{Intake (µg/d)} = \text{Water Conc. (ng/L)} \times \text{BCF (L/kg)} \times \text{Fish Ingestion (kg/d)} \times 10^{-3} \text{ µg/ng}
\] [5]

where the water concentration (in ng/L) is the measured concentration of PBLx in both ocean and surface water, BCF is the bioconcentration factor relating PBLx concentration in fish tissue (ng/kg), to PBLx concentration in water (ng/L) and fish ingestion (in kg/d) refers to the yearly-averaged daily human intake of fish from either ocean or surface water bodies. Because our period of assessment is one year, the exposure duration and averaging time are assumed equal. Moreover, because we are interested in long-term cumulative intake during this one-year period, we assume the exposure frequency is 365 d/year.

11.3.4 - Parameter values and data

The data needed for this exposure assessment include surface water concentrations based on limited monitoring data from fresh and ocean water, laboratory-scale BCF experiments, and activity patterns (variation in long-term average fish consumption). We also have biomonitoring data derived from limited geographical, temporal, and population subgroup coverage.

Table 11.1 summarizes the surface water concentration data available for making an estimate of the magnitude and range of fresh and ocean water concentrations of PBLx. Figure 11.2 provides a probability plot in which the cumulative distribution as reflected in the Z score is plotted against water concentrations for both surface and ocean water.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Total Number of samples</th>
<th>Number of samples &gt; LOD</th>
<th>Limit of detection (LOD) ng/L</th>
<th>Conc. range (ng/L)</th>
<th>Median Conc. (ng/L)</th>
<th>Surface water type</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBLx</td>
<td>16</td>
<td>6</td>
<td>9</td>
<td>&lt;LOD to 150</td>
<td>15.5</td>
<td>Fresh water</td>
</tr>
<tr>
<td>PBLx</td>
<td>35</td>
<td>14</td>
<td>9</td>
<td>&lt;LOD to 200</td>
<td>20</td>
<td>Ocean</td>
</tr>
</tbody>
</table>

The value of a quantitative uncertainty analysis depends on the care given to the process of constructing probability distributions. The processes of constructing a distribution from limited and imprecise data can be highly subjective. This process becomes more objective as the amount of data for a given parameter increases. However, a large set of data does not necessarily imply the existence of a suitable distribution function.

Based on the data summarized in Table 11.1 and Figure 11.2, we are required to make assumptions to complete our uncertainty analysis. The number of positive samples, within the limit of detection, is low for both ocean and surface water. In order to develop a probability distribution as well as moments (mean, standard deviation) for our analysis we must consider some method to represent observations below the LOD. We construct a cumulative probability plot under the assumption that values below the LOD provide an estimate of the cumulative
number of sample values above the LOD. This allows us to combine the ocean and freshwater samples so as to construct a probability distribution to fit these observations. This process is illustrated in Figure 11.2.

**Figure 11.2.** Probability plot showing the distribution of water sample concentration data in oceans and freshwater and the lognormal distribution used to represent these concentration data.
When constructing input distributions for an uncertainty analysis, it is often useful to present the range of values in terms of a standard probability distribution. It is important that the selected distribution be matched to the range and moments of any available data. Commonly used standard probability distributions include the normal distribution, lognormal distribution, uniform distribution, loguniform distribution, triangular distribution, beta distribution, gamma distribution, and logistic distribution. Modelers use various subjective, graphical, and statistical methods to select an appropriate distribution to represent a set of input values. In the probability plot provided in Figure 11.2, we can graphically compare how well the standard normal or standard lognormal distribution fit the set of concentration observations. Here we see a much better fit of the observations with a lognormal distribution. Statistical goodness-of-fit tests confirm that the lognormal distribution best fits these data.

In Table 11.2, we summarize the statistical moments (arithmetic mean and standard deviation, coefficient of variation, and geometric mean and geometric standard deviation) of the lognormal distribution used to represent the combined distribution of ocean and freshwater samples.

**Table 11.2. Statistical moments for model parameters in each scenario**

<table>
<thead>
<tr>
<th>Input Parameters</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>CV</th>
<th>Geometric Mean</th>
<th>Geometric Std. Dev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water Conc.(ng/L)</td>
<td>30.9</td>
<td>37.1</td>
<td>1.20</td>
<td>16.4</td>
<td>3.0</td>
</tr>
<tr>
<td>BCF L/kg</td>
<td>12,700</td>
<td>13,500</td>
<td>1.07</td>
<td>7,700</td>
<td>3.1</td>
</tr>
<tr>
<td>Human Ingestion of Fish (kg/d)</td>
<td>0.00034</td>
<td>0.00057</td>
<td>0.17</td>
<td>0.00033</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Fish BCF distributions for PBLx were constructed from data collected at six different laboratories where experimental measurements were carried out on multiple fish species. The range of measured BCF values are displayed in Table 11.3 along with information on the fish species used and laboratory where the experiments were carried out.

The data in Table 11.3 were used to construct a lognormal distribution of variation in these BCF values. We consider this variation to represent the uncertainty about what BCF value to apply to the surface water concentrations to translate the water concentration to a fish concentration. In Figure 11.3, we plot the cumulative number of measurements expressed as Z score against the range of BCF values. We then draw a straight line through these points to obtain the lognormal distribution that best fits this range of BCF values. The statistical moments of this line are summarized in Table 11.2.
Table 11.3. BCF data for PBLx in fish

<table>
<thead>
<tr>
<th>Log(BCF)</th>
<th>Fish type</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>fathead minnow (Pimephales promelas)</td>
<td>Laboratory 1</td>
</tr>
<tr>
<td>3.25</td>
<td>guppies (Poecilia reticulata)</td>
<td>Laboratory 2</td>
</tr>
<tr>
<td>3.31</td>
<td>rainbow trout (Salmo gairdneri)</td>
<td>Laboratory 3</td>
</tr>
<tr>
<td>3.4</td>
<td>rainbow trout (Salmo gairdneri)</td>
<td>Laboratory 3</td>
</tr>
<tr>
<td>3.55</td>
<td>channel catfish (Ictalurus punctatus)</td>
<td>Laboratory 1</td>
</tr>
<tr>
<td>3.6</td>
<td>fathead minnow (Pimephales promelas)</td>
<td>Laboratory 3</td>
</tr>
<tr>
<td>3.85</td>
<td>fathead minnow (Pimephales promelas)</td>
<td>Laboratory 3</td>
</tr>
<tr>
<td>3.95</td>
<td>mosquito fish (Gambusia affinis)</td>
<td>Laboratory 4</td>
</tr>
<tr>
<td>4.11</td>
<td>rainbow trout (Salmo gairdneri)</td>
<td>Laboratory 5</td>
</tr>
<tr>
<td>4.2</td>
<td>guppies (Poecilia reticulata)</td>
<td>Laboratory 5</td>
</tr>
<tr>
<td>4.3</td>
<td>rainbow trout (Salmo gairdneri)</td>
<td>Laboratory 6</td>
</tr>
<tr>
<td>4.43</td>
<td>No specific species described</td>
<td>Laboratory 6</td>
</tr>
<tr>
<td>4.5</td>
<td>rainbow trout (Salmo gairdneri)</td>
<td>Laboratory 6</td>
</tr>
<tr>
<td>4.7</td>
<td>goldfish (Carassius auratus)</td>
<td>Laboratory 6</td>
</tr>
</tbody>
</table>

Figure 11.3. Probability plot showing the distribution of measured BCF values and the lognormal distribution used to represent the variation in these measured values.

In order to illustrate the variation of fish ingestion for the case study, we use U.S. population fish ingestion rates taken from Ruffle et al. (1994), who examined variation of fish ingestion by adults in the US. They used a lognormal distribution to represent this fish-ingestion variation. The statistical moments of this distribution are summarized in Table 11.2.
11.3.5 – Worst case scenario

In order to contrast an uncertainty analysis with what is often common practice in risk assessment, we consider first the worst-case scenario. For the fish intake exposure pathway in our case study, the worst case would be the person who consumes the most fish, eating fish with the highest observed BCF taken from a water supply with the highest observed concentration of PBLx. The highest observed concentration of PBLx is 200 ng/L. The highest observed log BCF in the reported experiments is 4.7 with a corresponding BCF of 50,100. We then consider the highest continuous fish consumption as the 95% upper confidence limit on fish consumption in the reported data, a value of 0.00051 kg/d. Combining these values in our exposure equation (Equation 5) gives a worst-case scenario intake of 5.5 µg/d PBLx.

11.3.6 - Variance propagation

In order to determine variation in PBLx intake resulting from the variance (due to uncertainty and variability) in the parameters used to describe the source-to-dose model, we first use the analytical method to propagate model variance in Equation 2 using moments taken directly from Table 11.2. We then make use of the data in Table 11.2 to set up factorial design, DPD, Monte Carlo sampling and Latin Hypercube Sampling (LHS) simulations. In the factorial design approach, we used three values to represent the distribution of each of three inputs, yielding 27 combinations of "Low", "Medium" and "High". As prescribed by the method, "Medium" describes the median of the parameter value range; and "High" and "Low" represent the observed upper and lower extremes. In the case of fish intake, however, original data were not available. "High" and "Low" values were set to represent values at three standard deviations from the means. The high, medium, and low values used in the factorial design analysis are listed in Table 11.4.

Table 11.4. Factorial-design method values

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water Concentration (ng/L)</td>
<td>5</td>
<td>20</td>
<td>200</td>
</tr>
<tr>
<td>BCF (L/kg)</td>
<td>1,300</td>
<td>7,500</td>
<td>50,000</td>
</tr>
<tr>
<td>Fish Intake (kg/d)</td>
<td>0.00017</td>
<td>0.00034</td>
<td>0.00051</td>
</tr>
</tbody>
</table>

For the DPD method, as for the factorial design example above, we used three input variables and a "High", "Medium" and "Low" value to represent each input distribution. The values used to represent these ranges are listed in Table 11.5. In the DPD case, the "High" and "Low" values were calculated as the median values of the upper and lower 33\textsuperscript{rd} percentiles of the lognormal distributions used to represent the variance of the input parameters. The "Medium" value was set at the median value of each input distribution.

Table 11.5. DPD method input values

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water Concentration (ng/L)</td>
<td>5.4</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>BCF (L/kg)</td>
<td>2,500</td>
<td>7,500</td>
<td>24,000</td>
</tr>
<tr>
<td>Fish consumption kg/d</td>
<td>0.00028</td>
<td>0.00034</td>
<td>0.00039</td>
</tr>
</tbody>
</table>
11.3.7 - Variance propagation with uncertainty and variability combined

Model variance was propagated using the factorial, DPD, MC and LHS methods. Table 11.6 provides a summary comparison of the outputs from each method. Table 11.6 provides the arithmetic mean, arithmetic standard deviation, coefficient of variation (CV), geometric mean, geometric standard deviation, 5th percentile, and 95th percentile outcomes obtained from each method.

Table 11.6. Moments of the intake distribution obtained from different model variance propagation methods

<table>
<thead>
<tr>
<th></th>
<th>Analytical</th>
<th>Monte Carlo (2000)</th>
<th>LHS (200)</th>
<th>DPD</th>
<th>Factorial design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.13</td>
<td>0.13</td>
<td>0.14</td>
<td>0.081</td>
<td>0.5</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>0.36</td>
<td>0.28</td>
<td>0.29</td>
<td>0.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Coefficient of Variation (CV)</td>
<td>2.8</td>
<td>2.2</td>
<td>2.2</td>
<td>1.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Median/Geometric Mean (GM)</td>
<td>0.043</td>
<td>0.042</td>
<td>0.042</td>
<td>0.041</td>
<td>0.065</td>
</tr>
<tr>
<td>GSD</td>
<td>4.4</td>
<td>4.7</td>
<td>5.4</td>
<td>3.5</td>
<td>9.3</td>
</tr>
<tr>
<td>5th percentile</td>
<td>0.0037</td>
<td>0.0034</td>
<td>0.0021</td>
<td>0.0041</td>
<td>0.0015</td>
</tr>
<tr>
<td>95th percentile</td>
<td>0.49</td>
<td>0.52</td>
<td>0.54</td>
<td>0.38</td>
<td>2.2</td>
</tr>
</tbody>
</table>

The differences in estimation of these moments for each scenario are graphically illustrated in Figures 11.4, 11.5, and 11.6 where the cumulative density functions (CDF) obtained from each numerical variance propagation method are compared to the analytical results. The results of the analytical method are assumed to represent the true moments of the model output and therefore, the true CDF. Mean and standard deviation of ln(x) are used in plotting the analytical CDF. The equation for the transformation from arithmetic moments to the moments of ln(x) are as follows:

\[ \mu_l = \text{mean of ln} (x) = \ln \mu - 0.5 (\sigma_l^2) \]  

\[ \sigma_l = \text{Std. Dev. of ln} (x) = \sqrt{\ln \left(1 + \frac{\sigma_x^2}{\mu^2}\right)} \]  

Figure 11.4 compares of the CDFs for intake obtained from factorial design and DPD methods with the exact analytical solution for the CDF of intake. The 27 data points from the DPD and Factorial methods were used to plot the empirical CDF shown in Figure 11.4. Figure 11.5 compares the CDF for intake obtained from 2000 Monte Carlo (MC) simulations with the exact analytical solution for the CDF of intake. Figure 11.6 compares the CDF obtained from 200 Latin Hypercube Sampling Monte Carlo (LHS) simulations with the exact analytical solution.
solution for the CDF of intake. The MC and LHS empirical CDFs were plotted using all simulation outcomes.

**Figure 11.4.** Comparison of the Cumulative Density Functions (CDFs) for intake obtained from factorial design and DPD methods with the exact analytical solution for the CDF of intake and with the worst-case scenario.

**Figure 11.5.** Comparison of the CDF for intake obtained from 2000 Monte Carlo (MC) simulations with the exact analytical solution for the CDF of intake.
Figure 11.6. Comparison of the CDF for intake obtained from 200 Latin Hypercube Sampling Monte Carlo (LHS) simulations with the CDF from the exact analytical solution for intake.
From Table 11.6 and Figure 11.5 and 11.6, we see that MC and LHS provide very good agreement both with respect to finding the appropriate moments of the outcome distribution and with respect to the graphical fit. In contrast the DPD and the factorial design methods are only effective in capturing preliminary estimates of the mid-range values and first estimates of the spread of the outcome distributions. The factorial design, because the highest and lowest observed values are typically used to represent the upper and lower segments of the distribution, provides a reasonable estimate of the distributional midpoint and range but overstates the variance, CV, and mean considerably. The DPD, while similar in approach to the factorial design, employs the true moments of each third of the distribution. This results in a more accurate representation of the linear range of the CDF (Figure 11.4). However, even for DPD the tails tend to deviate from those observed in the analytical, LHS or MC approaches. This is due, primarily, to the limited number of segments used to represent input distributions and contributes to the underestimation of variance. Theoretically, calculation using more quantiles in either the DPD or factorial methods would improve the output representation, however, computational complexity increases geometrically with each additional segment used to represent inputs for these methods. In contrast to the approximate analytical solutions (factorial design and DPD), the MC and LHS both tend to track the “true” (analytical) outcome distribution quite well.

Comparing all of the distribution results to the “worst-case” scenario gives insight on the problem of using a worst-case scenario. In comparison to the results in Table 11.6 and Figures 11.4 through 11.6, the worst-case intake (5 µg/d) is an order of magnitude higher than the 95% upper confidence limit value of intake obtained from the analytical, Monte Carlo, LHS, and DPD arithmetic methods. The worst case result is even significantly higher than the upper 95th percentile outcome from the factorial design—an approach shown above to significantly overestimate the upper ranges of exposure relative to the analytical (exact) variance propagation method.

This relatively simple model illustrates the viability of the straightforward analytical analysis. Most models, unfortunately, involve many more input variables and proportionally more complex formulae to propagate variance. Fortunately, the LHS and MC methods simplify complex model variance analysis.

### 11.3.8 - Variance propagation with uncertainty and variability separated

So far in the case study, we focused on variance propagation methods and have not made an effort to distinguish between the relative contributions to overall variance from uncertainty and variability. In the examples above, the cumulative distributions presented in figures all reflect overall variance that includes the combined contributions from both uncertainty and variability. So out last step is to illustrate a two dimensional analysis in which we distinguish and display separate contributions from uncertainty and variability. We begin this analysis by going back to our inputs and assessing the relative contributions from uncertainty and variability.
First we consider the concentration, $C_w$, of PBLx in surface water. Earlier in this chapter, we showed that the observed ocean and freshwater data for concentration could be fit to a lognormal distribution. But we recognized that in the context of the exposed population, there is variability in this parameter attributable to spatial and seasonal variability as well as uncertainty due to measurement error and due to the representativeness of the sample size. Thus, the standard deviation observed in Figure 11.2 includes variance due to both variability and uncertainty. We assume now that we have conducted an evaluation that indicates that only 30 percent of the observed variance is due to variability and the remaining 70 percent of the observed variance is attributable to uncertainty. This evaluation is carried out by Monte Carlo simulation of the experimental method. That is, we consider how much variance due to measurement error and due to small sample size we would observe for any set of observations of the same concentration. We then simulate a set of observations that have a range of values for samples that were at the same concentration. We then use Monte Carlo sampling from the log normal distribution shown in Figure 11.2 to obtain a second set with the same number of observations. Using rank correlation to compare the spread of observations from a set of samples all the same concentration with a set of samples selected from the distribution in Figure 11.2, find that 30 percent of the full variance is explained by variation in observing a single value. Because the log normal distribution in Figure 11.2 has both true variability and uncertainty, the concentration data can be represented by a family of distributions with a variance with GSD of 1.64 due to variability. These curves have a location range that spans a range with a GSD of 2.51. This is illustrated in Figure 11.7. Here we see that when uncertainty is separated from variability the result is a range of curves reflecting variability at different confidence levels with respect to uncertainty. In this example we make all curves go through the same median point so that all curves of variability have the same geometric mean. With this approach we impose uncertainty on the variance of concentration but not on the geometric mean. It is more typical to use a set of curves that have different means and variance to better map out uncertainty about range of curves that can fit these observations.

Next we consider the bioconcentration factor, BCF, of PBLx. Earlier in this chapter, we used results from series of experiments to develop for BCF a probability distribution that includes both variability and uncertainty. Again an assumed evaluation of the data and measurements indicates that only 40 percent of the observed variance is due to variability and the remaining 60 percent of the observed variance is attributable to uncertainty. So the concentration data consist of a family of distributions with a variance having GSD of 1.93 due to variability. These curves have a location range that spans a range with GSD of 2.37.
Finally, we consider the data on fish ingestion data. Here we note that essentially all of the variance in the probability distribution used to represent observations on fish consumption reflect variability. So in this case, the curve reflecting both variability and uncertainty is assumed to be the same as the curve reflecting variability.

We now repeat our Monte Carlo assessment using a nested approach that separates out uncertainty and variability. For both Cw and BCF we simulate uncertainty by selecting a factor from a lognormal distribution with a GM of 1 and a GSD of 2.51 and 2.37 respectively. This factor is applied to each estimate of intake that is obtained from Monte Carlo sampling from the distributions of variability only for Cw, BCF, and fish ingestion. This process generates one curve of variability for each outer loop with a selected GSD for uncertainty in Cw and BCF. The results of this process are illustrated in Figure 11.8, which shows examples of the curves that can be plotted from this type of nested Monte Carlo analysis.
Figure 11.8. Examples of the curves that can be plotted from this type of nested Monte Carlo analysis

Figure 11.8 illustrates the results of a nested, two-dimensional quantitative uncertainty assessment. In Figures 11.4 through 11.6 we presented the results of an uncertainty assessment by allowing the variance in each parameter to be represented by a single distribution with a range and standard deviation that represents both variability (heterogeneity) and true uncertainty. Now we recognize that, for each parameter, some of the observed variance is due to uncertainty and some due to variability and separate out these components. Figure 11.6 shows the results of making this separation. For reference, the thick grey line show a cumulative distribution of intake when uncertainty and variability in each parameter are combined—as was obtained in Figures 11.4 through 11.6. The other curves are examples of cumulative distributions of variability that result at different levels of uncertainty. When we make 1000 outer loop (uncertainty) calculations by Monte Carlo sampling from the distributions of uncertainty for each parameter, we obtain 1000 cumulative distributions for variability. For each of these outer loop simulations we fix the selected uncertainty parameters and then run a second Monte Carlo assessment by randomly selecting from distributions of variability. The resulting set of 1000 cumulative distribution curves reflects both uncertainty and variability. We can order these curves from left to right based on the median value of intake obtained in each curve as illustrated in Figure 11.8 with a small subset of these curves. From this set of 1000 curves, the 50th curve in the set would be the curve corresponding to the 5% lower confidence bound value of intake with respect to uncertainty at any given percentile of variability. The 500th curve in
the set would be the curve corresponding to the median intake value with respect to uncertainty at any given percentile of variability. The 95$^{th}$ curve in the set would be the curve corresponding to the 95% upper confidence bound with respect to uncertainty at any given percentile of variability. These select curves are identified for our case study in Figure 11.8.

11.4 – Summary of the case study
This case study addresses the problem of defining, characterizing, and propagating uncertainty in an exposure model. Uncertainty analysis is used to assess the impact of data precision on model predictions. A common complaint associated with “worst-case” approaches to risk assessment is that the use of highly conservative values for each input variable results in significant overestimation of actual risk and/or exposure factors.

Characterization and propagation of variance for input parameters does two things. First it gives the decision maker a more realistic view of how estimates can spread, given what is known about the inputs. Secondly, instead of a point value, variance propagation quantifies output certainty allowing assessment of its accuracy and usefulness. In this case study, we illustrate how different variance propagation methods make possible different levels of evaluation, depending on the information available, complexity of the model and the accuracy needed. The case study illustrates a strategy for evaluating the sources of uncertainty in predictive exposure assessments. The methods and examples presented make clear that risk managers should be aware of the uncertainty in risk estimates and include this awareness in their decisions and their communications of risk to the public. As illustrated in the case study, one of the issues in uncertainty analysis that must be addressed is the need to distinguish between the relative contribution of true uncertainty versus variability (i.e., heterogeneity).

12 – Annex III: Application

12.1 - Introduction
The characterization of uncertainties (NA, Low, Medium and High) has been evaluated throughout the three-dimensional characteristics after having identified the sources of uncertainty and their relative values according to the source document “Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds”, part III of the U.S. EPA 2003, authored by Farland, W.H.; Birnbaum, L.S.; Cleverly, D.H.; DeVito, M.J.; Lorber, M.N.; Rodan, B.D.; Schaum, J.L.; Tuxen, L.C. and Winters, D.L. EIS-ChemRisks Toolbox has been used to facilitate the systematic identification of the sources of uncertainty.

12.2 - Objective
This application has used chapter 3 on sources, chapter 4 on Tiering, chapter 5.1 on qualitative uncertainty and chapter 6 on communication.
This practical application has been prepared by members of the uncertainty assessment working group (i.e., Thomas McKone, Michael Schümann, Andy Hart, Alexandre Zenié and Gerhard Heinemeyer).

### 12.3 – Sources of uncertainty

Chapter 3 on the sources of uncertainty has highlighted three basic sources of uncertainty: scenario, model and parameters. The qualitative characterization method (section 5.1) focuses on the previously identified sources of uncertainty.

However, in the following context, the ‘aim’ of the exposure assessment is separately considered as a source of uncertainty separately from the other sources of uncertainty:

1. Possible disagreements between stakeholders
2. Ill-defined objectives
3. Inadequate framing of the exposure assessment

Similarly, the following analysis of the exposure assessment ‘output’ can be achieved when the output is considered as source of uncertainty separately from the other sources of uncertainty:

1. Providing a qualitative indication of the propagate of uncertainty throughout the assessment
2. Assessing how well the output and its way of presentation matches the defined aim and purpose of the assessment
3. Analysing how different interpretations and reviews of the output contribute to the overall uncertainty of the assessment

Although, we have characterized the uncertainty for the scenario, several scenario building elements were included too (e.g., target and geographic applicability). The scenario building elements are listed in the third column below. Finally, the considered sources are summarised in Table 12.1.

<table>
<thead>
<tr>
<th>Sources of uncertainty</th>
<th>Major</th>
<th>Detailed</th>
<th>Included</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aim</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Purpose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Issue at stake</td>
<td></td>
</tr>
<tr>
<td><strong>Scenario</strong></td>
<td></td>
<td>Source(s) / Product(s)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Agent / Chemical</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Generic Exposure Scenario</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Target / Subject</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Microenvironment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Geographic applicability</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seasonal applicability</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemical Release</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exposure Pathway</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exposure Event</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exposure Route(s)</td>
<td></td>
</tr>
</tbody>
</table>
12.4 – Selected Tier

This case study goes beyond using simple safety factors. Thus it is not Tier 0. All of the uncertainties have been characterized qualitatively, i.e. Tier 1. At this point, none of the sources have been treated deterministically nor probabilistically. So none of them is treated at a higher Tier (i.e., Tier 2, Tier 3).

Although it is not Tier 0, it does include many of the elements of Tier 0, but then moves on to Tier 1. This suggests that Tier 0 is a useful starting point but may not be an adequate ending point for any type of uncertainty analysis.

12.5 – Characterization of uncertainty

The assessors considered the individual and the combined subjectivity sources of uncertainty systematically. The uncertainties characterization has been evaluated throughout the three-dimensional characteristics: level of uncertainty, appraisal of the knowledge base and subjectivity of choices. Each of the last two characteristics has been decomposed into its five explicit criteria (see section 5.1) that are listed in the legend below. The results are shown in the following table (see Table 12.2):

<table>
<thead>
<tr>
<th>Conceptual model</th>
<th>Conceptual model</th>
<th>Conceptual model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathematical model</td>
<td>Formula</td>
<td></td>
</tr>
<tr>
<td>Parameters</td>
<td>Non Chemical specific</td>
<td>Non Chemical specific data</td>
</tr>
<tr>
<td>Chemical specific</td>
<td>Chemical specific data</td>
<td></td>
</tr>
<tr>
<td>Output</td>
<td>Calculation</td>
<td>Result(s)</td>
</tr>
</tbody>
</table>

Table 12.1. the considered sources of uncertainty
### Background Human Ingestion Exposure to PCBs through Freshwater and Marine Fish & Shellfish

**Source document:**

*Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds*

2003 - Part III

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#### EXPOSURE ASSESSMENT AIM

<table>
<thead>
<tr>
<th>Exposure Assessment aiming for:</th>
<th>Reasonably foreseeable use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stakeholder/Rapporteur of the source documents</td>
<td>National Center for Environmental Assessment Research and Development</td>
</tr>
<tr>
<td>Purpose</td>
<td>As a technical resource for use in proactive risk assessment.</td>
</tr>
<tr>
<td>Issue at Stake</td>
<td>Establishing background exposure for the United States region. Its purpose was characterizing population background of exposure based on the intake of randomly selected population.</td>
</tr>
</tbody>
</table>

**Level of Uncertainty**

**Low**

Simply because we set the goal.

**Appraisal of the Knowledge Base**

\[aNA + rLow + pMed + scMed + roNA\]

Limited data available for food consumption in general.

**Subjectivity of Choices**

\[cHigh + iapNA + islNA + scan + icrHigh\]

Because data is so limited we have to make assumptions.
| PRODUCT | EIS-ChemRisks source taxonomy:  
1. Foods  
2. Freshwater fish and shellfish  
Related source(s):  
1. Foods  
2. Marine fish and shellfish |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PRODUCT</td>
<td>Freshwater fish and freshwater shellfish and marine fish and marine shellfish</td>
</tr>
<tr>
<td>CHEMICAL</td>
<td>Polychlorinated biphenyl (PCB)</td>
</tr>
<tr>
<td>CHEMICAL</td>
<td>CAS Number: 1336-36-3</td>
</tr>
</tbody>
</table>

**Scenario**

Product categories are not harmonized.

**Level of Uncertainty**

**High**

We cannot trace back to the original (emission) sources. We do not have fully representative data.

**Appraisal of the Knowledge Base**

$$a_{High} + r_{Med} + p_{High} + s_{NA} + r_{Med}$$

We have general population data only. We don’t have details on consumption patterns. We don’t have data on variability within and over fish species. Reliable measurement i.e., analytical measurements on fish are Low but High for human fish consumption because too few sample and few data on human consumption behaviour. We are missing the description of variation among people, among region, among gender. This holds especially for possible high exposure groups (high fish consumption and high environmental concentration): see section 8.4.5 of the uncertainty chapter in volume 3 of part I. Predictability Low and dependency High. More data are required to get more predictability.

**Subjectivity of Choices**

$$c_{Med} + i_{apMed} + i_{slMed} + s_{High} + i_{crMed}$$

Subjective choices need to be made. Stakeholders’ subjectivity is Medium because we don’t know the emission and lack updated information. No funds for new sampling. Limited willingness to fill in the existing data gaps. Evaluation of the results somewhat depends on the input data and on the stakeholder point of view. We cannot make big changes to the answer. The choices are bounded by knowledge and by measurement.
The averaged fish and shellfish daily consumption is an extrapolation value taken from 24 hours recall protocols and thus introduces uncertainty concerning a daily uptake.

**Dietary activity**

- **Averaged eating fish and shellfish daily**
  - **More Info:** Even if people don’t eat fish and shellfish every day, we focused on long-term equivalent daily consumption

**Daily activity**

- **Eating fish and shellfish daily**

**TARGET**

- **Adult**
  - **Adults**
    - **More Info:** randomly selected individuals from a large region population such as the United States

**ENV**

- **Not applicable**

**GEO**

- **Specific country(ies)**
  - **UNITED STATES**

**SEAS**

- **Autumn Spring Summer Winter**

---

**Level of Uncertainty**

- **High**
  - We cannot trace back to the original (emission) sources. We do not have fully representative data.

**Appraisal of the Knowledge Base**

- **aHigh + rMed + pHigh + scNA + roMed**
  - We only have general population data. We don’t have details on consumption patterns. We don’t have data on variability within and over fish species. Reliable measurement *i.e.*, analytical measurements on fish are Low but High for human fish consumption because of too few samples and few data on human consumption behaviour.
  - We are missing the description of variation among people, among region, among gender. This holds especially for possible high exposure groups (high fish consumption and high environmental concentration): see section 8.4.5 of the uncertainty chapter in volume 3 of part I. Predictability Low and dependency High. More data are required to get more predictability.

**Subjectivity of Choices**

- **csMed + iapMed + islMed + scHigh + icrMed**
  - Subjective choices need to be made. Stakeholders’ subjectivity is Medium because we don’t know the emission and lack updated information.
  - No funds for new sampling. Limited willingness to fill in the existing data gaps.
  - Evaluation of the results somewhat depends on the input data and on the stakeholder point of view. We cannot make big changes to the answer. The choices are limited by knowledge and by measurement.

Eating behaviour of people may change seasonally.
## Chemical Release, Exposure Pathway, Event & Routes

<table>
<thead>
<tr>
<th>Qualitative Characterization:</th>
<th>Level of Uncertainty</th>
<th>Appraisal of the Knowledge Base</th>
<th>Subjectivity of Choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration of PCBs in fresh and marine water are taken up by fish and shellfish and then transferred to human by consumption of fish and shellfish.</td>
<td><strong>High</strong></td>
<td>We cannot trace back to the original (emission) sources. We do not have fully representative data.</td>
<td><strong>csMed + iapMed + islMed + scHigh + icrMed</strong></td>
</tr>
<tr>
<td><strong>Quantitative Information:</strong></td>
<td></td>
<td>We have general population data only. We don’t have details on consumption patterns. We don’t have data on variability within and over fish species. Reliable measurement i.e., analytical measurements on fish are Low but High for human fish consumption because of too few samples and few data on human consumption behaviour. We are missing the description of variation among people, among region, among gender. This holds especially for possible high exposure groups (high fish consumption and high environmental concentration): see section 8.4.5 of the uncertainty chapter in volume 3 of part I. Predictability Low and dependency High. More data are required to get more predictability.</td>
<td></td>
</tr>
<tr>
<td>• Field surveys of freshwater fish and shellfish PCB concentrations. Field surveys of marine fish and shellfish PCB concentrations.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Per capita, adult average consumption of freshwater fish and shellfish. Per capita, adult average consumption of marine fish and shellfish.</td>
<td></td>
<td>Subjective choices need to be made. Stakeholders’ subjectivity is Medium because we don’t know the emission and lack updated information. No funds for new sampling. Limited willingness to fill in the existing data gaps. Evaluation of the results somewhat depends on the input data and on the stakeholder point of view. We cannot make big changes to the answer. The choices are limited by knowledge and by measurement.</td>
<td></td>
</tr>
<tr>
<td>Adult body weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure Pathway</td>
<td>Transfer of chemicals from freshwater and marine water into fish and shellfish and then into consumed fish and shellfish. We exclude aquacultured fish.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STEP 1:</strong></td>
<td>Chemicals in marine and freshwater environment</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STEP 2:</strong></td>
<td>Chemicals transferred from water and fish diet to fish through bio-uptake (bio-concentration and/or bio-accumulation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STEP 3:</strong></td>
<td>Fish is transferred from water to plate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STEP 4:</strong></td>
<td>Ingestion of fish by consumers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Exposure Event   | Consuming freshwater fish, freshwater shellfish, marine fish and marine shellfish.                                                |

| Exposure Routes  | Oral exposure                                                                                                                  |

| Many steps are hidden between water and plate (e.g., supermarket, household cooking, frying). |
| Level of Uncertainty | We cannot trace back to the original (emission) sources. We do not have fully representative data. |

| Appraisal of the Knowledge Base | We have general population data only. We don’t have details on consumption patterns. We don’t have data on variability within and over fish species. Reliable measurement i.e., analytical measurements on fish are Low but High for human fish consumption because of too few samples and few data on human consumption behaviour. We are missing the description of variation among people, among region, among gender. This holds especially for possible high exposure groups (high fish consumption and high environmental concentration): see section 8.4.5 of the uncertainty chapter in volume 3 of part 1. Predictability Low and dependency High. More data are required to get more predictability. |

| Subjectivity of Choices | Subjective choices need to be made. Stakeholders’ subjectivity is Medium because we don’t know the emission and lack updated information. No funds for new sampling. Limited willingness to fill in the existing data gaps. Evaluation of the results somewhat depends on the input data and on the stakeholder point of view. We cannot make big changes to the answer. The choices are limited by knowledge and by measurement. |

|                      |                                                                 |
## Conceptual Model

Two-input exposure model is used. They are: fish concentration and fish ingestion. We assume that there is no change in concentration from measurement of the whole fish and the fish consumed in a meal. Furthermore, we assume that the measurement of gram fish ingested per kg body weight is the relevant parameter to represent ingestion.

### Level of Uncertainty

**Med**

The concept should depend of variation of PCB content between species.

### Appraisal of the Knowledge Base

**aNA + rLow + pLow + scNA + roLow**

Because the model is in simple form consistent with existing knowledge the uncertainty is low with respect to existing data knowledge. We acknowledge the ignorance to restrict the complexity. We try to maximize predictability using maximum simplicity. It is easier to predict “how many days it will rain in May” than “giving an estimate if it is raining next Tuesday”.

### Subjectivity of Choices

**csMed + iapMed + islNA + scNA + icrHigh**

Subjectivity is Medium because some choices (whatever consumption is dependent or not on body weight and gender) are made. Stakeholders could lobby for different choices, e.g., ages, consumption. If you select a different concept, e.g., time series versus steady state the results will change a lot.

## Mathematical Model

PCB fish ingestion (Concentration * Ingestion Rate) / Body Weight

### Level of Uncertainty

**High**

The model ignores concentration changes from live fish to cooked meal (see steps of pathway).

### Appraisal of the Knowledge Base

**aLow + rLow + pLow + scLow + roLow**

The knowledge base supports the concept mathematically. The formula fits well the limited exiting data.

### Subjectivity of Choices

**csNA + iapNA + islNA + scLow + icrLow**

Subjectivity is Low. Human errors and lack of review can influence the results. Influence of choices on results is Low because we expect a high level of reviewing.
### Non Chemical-Specific Exposure Data

#### Dietary Intake Factors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Data Source</th>
<th>Level of Uncertainty</th>
<th>Appraisal of the Knowledge Base</th>
<th>Subjectivity of Choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish and Shellfish Consumption Rates</td>
<td><strong>5.9 [g/d] (arithmetic mean)</strong></td>
<td>Estimated Per Capita Fish Consumption in the United States 2003 - PA-821-C-02-003)</td>
<td>High</td>
<td>The knowledge base is Medium because a great deal of information is missing. Accurate because of what it represents. Reliable in the context of what it represents. Plausibility is Low because of questionable applicability to different populations. Robustness is Medium because of the dependency on body weight for example.</td>
<td>Subjectivity is Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>There may be variability between countries and regions but the methodology is highly agreed.</td>
</tr>
<tr>
<td>Fish and Shellfish Consumption Rates</td>
<td><strong>9.6 [g/d] (arithmetic mean)</strong></td>
<td>Estimated Per Capita Fish Consumption in the United States 2003 - PA-821-C-02-003)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Weight</td>
<td><strong>70 [kg] (default)</strong></td>
<td>this source document</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Anthropometric/Physiological Parameters

**Body Weight**
Mean adult body weight

Data source:

- This part has been omitted!
- The standard value is questionable because of changes over time and a low degree of representativity for the US target population. It is not a major source of uncertainty: see table 8.1 of the uncertainty chapter in volume 3 of part I.
### Chemical-Specific Exposure Data

<table>
<thead>
<tr>
<th>(Oral exposure) Exposure concentration</th>
<th>Data source: this source document</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Freshwater fish and shellfish concentration</strong></td>
<td><strong>Note:</strong> This number is the dioxin toxic equivalent expressed in TEQ_{p-\text{WHO}98}</td>
</tr>
<tr>
<td><strong>1.2 [pg/g] (arithmetic mean)</strong></td>
<td></td>
</tr>
<tr>
<td>(\text{Level of Uncertainty} )</td>
<td><strong>High</strong></td>
</tr>
<tr>
<td><strong>The value is single for a multiple dimension (e.g., fish species and fish size) parameter</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(Oral exposure) Exposure concentration</th>
<th>Data source: this source document</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Marine fish and shellfish concentration</strong></td>
<td><strong>Note from the source document:</strong> This number is the dioxin toxic equivalent expressed in TEQ_{p-\text{WHO}98}</td>
</tr>
<tr>
<td><strong>0.25 [pg/g] (arithmetic mean)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Appraisal of the Knowledge Base</strong></td>
<td><strong>aMed + rHigh + pMed + scMed + roMed</strong></td>
</tr>
<tr>
<td><strong>The knowledge base is Medium because a great deal of information is missing. Accuracy is limited by the sample size. Reliability is high because it is transformed. It does not cover all PCBs and has a weighting factor building in it. Plausibility is Medium because of what it represents. Scientific consistency is Medium because of the set of transformations factors inherent in the TEQ calculation. Robustness is Medium because of the dependency on TEQ.</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Subjectivity of Choices</strong></th>
<th><strong>Subjectivity is High because of the choice of TEQ. Different stakeholders will have different TEQs. Laboratory analysis influence of the value.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>csHigh + iapHigh + isINA + scMed + icrMed</strong></td>
<td></td>
</tr>
</tbody>
</table>
### EXPOSURE ASSESSMENT RESULTS

Total consumption of fish and shellfish = consumption of freshwater fish and freshwater shellfish + consumption of marine fish and marine shellfish

\[ \frac{(1.2 \times 5.9)}{70} + \frac{(0.25 \times 9.6)}{70} = 0.135 \]

- **Intake per body weight per day**
  - from freshwater fish, freshwater shellfish, marine fish and marine shellfish

<table>
<thead>
<tr>
<th>0.135 [pg/kg.d] (arithmetic mean)</th>
<th>Note from the source document: This number is the dioxin toxic equivalent expressed in TEQ&lt;sub&gt;p&lt;/sub&gt;-WHO&lt;sub&gt;98&lt;/sub&gt;</th>
</tr>
</thead>
</table>
| **Level of Uncertainty**
  - High |
  - Because the inputs are high and the concept too. |
| **Appraisal of the Knowledge Base**
  - aHigh + rHigh + pHigh + scHigh + roHigh |
  - The knowledge base supports the formula but it is very hard to check the result. Non validatable result |
| **Subjectivity of Choices**
  - csNA + iapNA + islNA + scNA + icrNA |
  - Subjectivity is NA because it is driven by upstream decisions. |

**Comments**

- Study case chapter for the WHO report entitled "Guidance Document on Characterizing and Communicating Uncertainty of Exposure Assessment"

---

Note that the “Risk Management Measures” is omitted because it is not applicable for uncertainty characterization.

Note that the uncertainties characterisation for the scenario source is unique for all eleven elements building the scenario (i.e., product, chemical, gen. exp. scen., target, env, geo, seas, emission, pathway, event and routes) but has been split to clarify the presentation. Some scenario elements are abbreviated as following: “GEN. EXP. SCEN.” stands for “Generic Exposure Scenario”, “ENV” stands for “Microenvironment”, “GEO” stands for “Geographic Applicability” and “SEAS” stands for “Seasonal Applicability”.

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Note that each source of uncertainty has a title, a value, a justification of the value eventually, characterization of uncertainties according to three dimensions (i.e., red, orange and purple) and a justification of each characterization in separate columns. Some lines are added without any characterization of uncertainty for the clarity of the test case.

**Table 12.2.** The uncertainties characterization has been evaluated throughout the three-dimensional characteristics
The results are summarised in the following table (see Table 12.3):

<table>
<thead>
<tr>
<th>Sources of uncertainty</th>
<th>Characteristics of uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Level of Uncertainty</td>
</tr>
<tr>
<td>Aim</td>
<td>Low</td>
</tr>
<tr>
<td>Scenario</td>
<td>High</td>
</tr>
<tr>
<td>Conceptual model</td>
<td>Medium</td>
</tr>
<tr>
<td>Mathematical model</td>
<td>High</td>
</tr>
<tr>
<td>Parameters</td>
<td>High</td>
</tr>
<tr>
<td>Results</td>
<td>High</td>
</tr>
</tbody>
</table>

**Table 12.3. summary of the uncertainty characterization**

As part of this exercise, the assessors subjectively considered the extent to which the different uncertainties may interact.

It is clear from the source document that the processes affecting the exposure are much more complex than the conceptual model and that a more complex conceptual model could have been devised. But the assessors chose to make it simple due to limitation in knowledge about the detailed processes and parameters.

Therefore, although the uncertainty of the conceptual model was characterized as “Medium” when considered in isolation, the assessors concluded that the uncertainty of subsequent parts of the uncertainty characterization (i.e., formula, parameters and results) was primarily caused by the conceptual model.

Overall, the assessors concluded that the uncertainty is “High” and the overall biggest contributor is the conceptual model.

**12.6 - Communication**

**12.6.1 – Communication to other scientists**

The estimate of the exposure is 0.135 pg/kg.d. Normally, this value is communicated with an estimate of toxicity.

The assessors considered systematically the individual and the combined subjectivity sources of uncertainty. The results are shown in the following table:
As part of this exercise, the assessors subjectively considered the extent to which the different uncertainties may interact.

It is clear from the source document that the processes affecting the exposure are much more complex than the conceptual model and that a more complex conceptual model could have been devised. But the assessors chose to make it simple due to limitation in knowledge about the detailed processes and parameters.

Therefore, although the uncertainty of the conceptual model was characterized as “Medium” when considered in isolation, the assessors concluded that the uncertainty of subsequent parts of the uncertainty characterization (i.e., formula, parameters and results) was primarily caused by the conceptual model.

Overall, the assessors concluded that the uncertainty is “High” and the overall biggest contributor is the conceptual model.

The detailed table is annexed (see Table 12.2).

12.6.2 – Communication for the risk managers

The exposure of the American population to dioxin-like PCBs has been assessed by a group of internationally recognised experts convened by the U.S. EPA. The estimate of the exposure is 0.135 pg/kg.d. Normally, this value is communicated with an estimate of toxicity.

Overall, the assessors concluded that the uncertainty is “High” and the overall biggest contributor is the very simplified model used to represent complex mechanisms and scenarios of exposure.

The estimated exposure result is based on some conservative assumptions, so it may be conservative but it is not possible to specify how conservative it is. In other words, it is probable that the majority of the population receive lower exposure than the estimate. But it is possible that some unknown percentage of people will be exposed above the estimated results.

Annex

The assessors considered systematically the individual and the combined subjectivity sources of uncertainty. The results are shown in the following table:

<table>
<thead>
<tr>
<th>Sources of uncertainty</th>
<th>Level of Uncertainty</th>
<th>Appraisal of Knowledge Base</th>
<th>Subjectivity of Choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scenario</td>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conceptual model</td>
<td>Medium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mathematical model</td>
<td>High</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Parameters</td>
<td>High</td>
<td>High</td>
<td>NA</td>
</tr>
<tr>
<td>Results</td>
<td>High</td>
<td>High</td>
<td>NA</td>
</tr>
</tbody>
</table>
As part of this exercise the assessors considered subjectively the extent to which the different uncertainties may interact.

It is clear from the source document that the processes affecting the exposure are much more complex than the conceptual model and that a more complex conceptual model could have been devised. But the assessors chose to make it simple due to limitation in knowledge about the detailed processes and parameters.

Therefore, although the uncertainty of the conceptual model was characterized as “Medium” when considered in isolation, the assessors concluded that the uncertainty of subsequent part of the uncertainty characterization (i.e., formula, parameters and results) was primarily caused by the conceptual model.

Overall, the assessors concluded that the uncertainty is “High” and the overall biggest contributor is the conceptual model.

12.6.3 - Communication for the public

The exposure of the American population to dioxin-like PCBs\(^1\) has been assessed by a group of internationally recognised experts convened by the U.S. EPA. The estimate of the exposure is 0.135 pg/kg.d. Normally, this value is communicated with an estimate of toxicity.

The majority of the population receive lower exposure than the estimate. But it is possible that some unknown percentage of people will be exposed above the estimated results.

The above statement summarises the outcomes of the exposure assessment. In order to give a balanced message to the public, it is important to accompany this statement with information about the risk management conclusions, for example:

Further investigations will be necessary to clarify the extent of exposure.

In the meanwhile, it is prudent to continue efforts/actions to progressively reduce the exposure levels to dioxin-like chemicals such as PCBs.

12.7 – Legends

12.7.1 – Legend of qualitative uncertainty analysis

- **LU**: Level of Uncertainty
  - a: accuracy
  - r: reliability
  - p: plausibility
  - sc: scientific consistency
  - ro: robustness

- **AKB**: Appraisal of the Knowledge Base
  - intersubjectivity among peers and among stakeholders
  - influence of situational limitations (e.g., money, tools and time) on choices
  - sensitivity of choices to the analysts' interests
  - influence of choices on results

---

\(^1\) For introduction and further information to dioxin-like PCBs see U.S. EPA (2001)
12.7.2 - Legend of units

- g  gram
- pg picogram
- d  day
- kg kilogram