Chapter 12
Uncertainty and Variability Issues in Public Health Risk Evaluation

Uncertainty and variability are almost an omnipresent aspect of risk assessments—and tackling these in a reasonably comprehensive manner is crucial to the overall risk assessment process. Broadly stated, *uncertainty* stems from lack of knowledge—and thus can be characterized and managed but not necessarily eliminated, whereas *variability* is an inherent characteristic of a population—inasmuch as people vary substantially in their exposures and their susceptibility to potentially harmful effects of exposures to the stressors of concern/interest (NRC 2009). In general, uncertainty can be reduced by the use of more or better data; on the other hand, variability cannot be reduced, but it can be better characterized with improved information. In any event, when all is said and done, uncertainty (alongside variability) analyses become key factors in the ultimate decision-making process that is typically developed to address chemical exposure problems. By way of probabilistic modeling and analyses, uncertainties associated with the risk evaluation process can be assessed properly and their effects on a given decision accounted for systematically. In this manner the risks associated with given decisions may be aptly delineated, and then appropriate corrective measures taken accordingly. This chapter discusses the key issues and evaluation modalities regarding uncertainty and variability matters that surround the overall risk assessment process.

12.1 Uncertainty and Variability Concerns in Risk Assessment

Risk assessments tend to be highly uncertain, as well as highly variable. In fact, due to the oftentimes limited availability of data for most scientific endeavors, uncertainty in particular tends to be rather pervasive in so many studies.

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Variability (or *stochasticity*) refers to the inherent lack of uniformity in a population—and this cannot be reduced with additional data, but can be better represented by providing ranges or distributions of the subject parameter in question; it arises from true heterogeneity or diversity in characteristics such as dose-response differences within a population, or differences in body weight, or differences in rates of food and water intakes/ingestion, or differences in chemical exposure levels in source materials, etc. Differences among individuals in a population are referred to as '*inter*-individual variability', and differences associated with a particular individual over time are referred to as '*intra*-individual variability'.

Uncertainty represents a lack of knowledge about factors such as adverse effects or chemical exposure levels—and this may potentially be reduced with additional studies or investigations. For instance, uncertainty in exposure estimates may be the result of limited data being available on significant exposure factors for a particular age group—or it may also be due to assumptions made in development of an exposure conceptual model; etc.

As an example of the intertwining relationships between uncertainty and variability, consider a situation involving the ingestion of contaminated drinking water; now, assume that it is possible to measure an individual's daily water consumption (and indeed the contaminant concentration) in exact terms—thereby eliminating uncertainty in the measured daily dose. Notwithstanding, the daily dose would still have an inherent day-to-day variability—due to changes in the individual's daily water intake, or the contaminant concentration in the water. Ultimately, since the individual's true average daily dose (ADD) is actually unknown, it becomes uncertain as to how close the estimate is to the true value. Accordingly, the variability across daily doses has been translated into uncertainty in the ADD. In this light, it becomes apparent that although the individual's true ADD has no variability *per se*, the estimate of the ADD has some uncertainty associated with it (USEPA 1997a, b, c, d, e, f, g, h). All together, uncertainty can indeed lead to inaccurate or biased estimates, whereas variability can affect the precision of the estimates and the degree to which they can be generalized.

On the whole, 'variability' encompasses any aspect of the risk assessment process that can produce varying results. This includes the potential interpretations of the available data, the availability of different data sets collected under different experimental protocols, and the availability of different models and methods—albeit several of these may also be considered as sources of uncertainty (NRC 1994a, b; USEPA 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h). Thus, the use of 'variability' to refer to differences attributable to diversity in biological sensitivity or exposure parameters means these differences can be better understood, but not reduced, by further research. On the other hand, 'uncertainty'—that refers to lack of knowledge about specific factors, parameters, or models—can generally be reduced through further study. Indeed, in principle, uncertainty can be reduced through the acquisition of more information, whereas variability is irreducible.

Finally, it is worth mentioning here that, some parameters used in risk assessments may reflect both variability and uncertainty under different sets of

circumstances or conditions. However, insofar as possible, stochastic variability and knowledge uncertainty should be segregated in the evaluation processes employed during the risk assessment. Ultimately, probabilistic assessments can become useful statistical tools for analyzing variability and uncertainty in risk assessments—particularly on the assumption that adequate data would be available for such undertaking.

12.1.1 Types and Nature of Variability

Three fundamental types of variability may be identified for most risk assessment exercises, namely (USEPA 1997a, b, c, d, e, f, g, h):

1. Spatial variability (i.e., variability across locations)
2. Temporal variability (i.e., variability over time)
3. Inter-receptor variability (i.e., variability amongst individual receptors)

Spatial variability can occur both at regional (macroscale) and local (microscale) levels. For example, fish intake rates can vary significantly depending on the region or locality of a country—with higher consumption more likely to occur among populations located near large water bodies or coastal areas (USEPA 1997a, b, c, d, e, f, g, h). In general, higher exposures tend to be associated with receptors in closer proximity to the pollutant source.

Temporal variability refers to variations that occur over time—and this may relate to both long- and short-term situations. For example, seasonal fluctuations in weather, pesticide applications, use of wood-burning appliances, and fraction of time spent outdoors relate to longer-term variability; and shorter-term variability may include differences in individual or personal activities on weekdays versus weekends, or even at different times of the day (USEPA 1997a, b, c, d, e, f, g, h).

Inter-receptor variability can be attributed or related to two major factors—namely: human characteristics (such as age or body weight) and human behaviors (such as location and activity patterns), each of which in turn may be related to several underlying phenomena that might vary as well (USEPA 1997a, b, c, d, e, f, g, h); for example, the natural variability in human weight may be attributed to a combination of genetic, nutritional, and other lifestyle or environmental factors. Congruently, it is notable that the common and significant 'inter-individual differences' in physical and pharmacokinetic characteristics include gender, body weight, rates of breathing, and metabolism; additionally, 'person-to-person differences' in behavioral attributes (such as dietary preferences, daily shower/bath duration, etc.) that govern route-specific exposures can be quite significant.

Variability may indeed be confronted and evaluated in a variety of ways (see, e.g., NRC 1994a, b; USEPA 1997a, b, c, d, e, f, g, h)—albeit a strategy that involves using both the appropriate maximum and minimum parameter values seems to be favored in most chemical exposure and risk assessments. Such approach allows for

the characterization of the variability by a range between the extreme values, as well as produces a measure of central tendency estimates.

12.1.2 Types and Nature of Uncertainty

Multiple sources of uncertainty exist in just about any type of risk evaluation. The uncertainties that typically arise in risk assessments can be of three general types—namely (see, e.g., USEPA 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h):

1. Uncertainties in parameter values (e.g., use of incomplete or biased values);
2. Uncertainties in parameter modeling (e.g., issue of model adequacy/inadequacy); and
3. Uncertainties in the degree of completeness (e.g., representativeness of evaluation scenarios).

Parameter uncertainties arise from the need to estimate parameter values from limited or inadequate data. Such uncertainties are inherent because the available data are usually incomplete, and the analyst must make inferences from a state of incomplete knowledge. Examples of uncertainties in parameter values relate to such issues as: incomplete or biased data; applicability of available data to the particular case on hand (i.e., generic vs. case-specific data); etc.

Modeling uncertainties stem from inadequacies in the various models used to evaluate hazards, exposures, and consequences—and also from the deficiencies of the models in representing reality. Examples of uncertainties in modeling relate to such issues as: model adequacy; whether uncertainty is introduced by the mathematical or numerical approximations that are made for convenience; use of models outside its range of validity; etc.

Completeness/scenario uncertainties relate to the inability of the analyst to evaluate exhaustively all contributions to risk. They refer to the problem of assessing what may have been omitted in the analysis. Examples of uncertainties in the degree of completeness may relate to such questions as to: whether the analyses have been taken to sufficient depth; whether all important hazard sources and exposure possibilities have been addressed; etc.

Depending on the specific aspect or component of the risk assessment being performed, the type of uncertainty that dominates at each stage of the analysis can be different. Anyhow, each type of uncertainty can be characterized either qualitatively or quantitatively. Various levels of uncertainty analysis can therefore be classified by the degree to which each type of uncertainty is quantitatively analyzed. Indeed, identification of the sources of uncertainty is an important first step in determining how to reduce the specific uncertainty. Furthermore, because the uncertainties tend to be fundamentally tied to a lack of knowledge concerning important evaluation factors/parameters, strategies for reducing uncertainty necessarily involve the concurrent reduction or elimination of knowledge gaps (USEPA 1997a, b, c, d, e, f, g, h).

Overall, uncertainties are inherent in just about all scientific undertakings—and this probably cannot be avoided. With that said, it should also be recognized that the extent to which uncertainties in data and analyses can be measured and expressed in highly quantitative terms depends very much on the types of investigations used to develop the scientific knowledge in the first place. For instance, highly controlled experiments, usually conducted in a laboratory or clinical setting, if well designed and conducted, can provide the clearest information regarding uncertainties—albeit it is still not always possible to quantify uncertainties in many experimental studies; indeed, controlled clinical trials, for example, still may come with uncertainties and variability that cannot necessarily be predicted or accurately quantified. As a matter of fact, using available knowledge with its inherent uncertainties to make predictions about an as-yet unobserved (and perhaps inherently unobservable) situation is even more uncertain—and yet such needs can be critical to the derivation of many important societal decisions (such as relates to human health protection efforts) (USEPA 2012). For instance, whereas, risk assessments can address such questions as to whether risk to health will be reduced if certain actions are taken, the scientific uncertainties associated with such predictive efforts include not only the uncertainty associated with the available knowledge, but also uncertainty related to the predictive nature of estimates.

Finally, it is noteworthy that uncertainty is invariably embedded in most risk evaluation processes. Indeed, many areas of science or scientific works involve uncertainty—and broadly speaking, uncertainty can become an obstacle to effective decision-making, i.e., unless effectually addressed. Anyhow, by acknowledging (and hopefully characterizing or addressing) uncertainty issues associated with a given project or undertaking, there just might be the chance of making a decision that would likely yield the greatest benefits for public health. Broadly stated in rather simplistic terms, the characterization of uncertainty during risk assessments generally implies that 'lower bounds', 'central estimates', and 'upper bounds' of risk can all be appropriately defined or identified and properly utilized in the risk-based decision-making processes—i.e., rather than a blind focus simply on so-called conservative or 'health protective' estimates of risk on only one end of the 'risk spectrum'. After all, uncertainty has to be seen more so as the characterization of our 'state of knowledge' of the problem on hand—and not as a barrier to effective decisions and actions. At any rate, for all practical purposes, uncertainties are generally propagated through the analysis under consideration. To the extent possible, a 'sensitivity analysis' provides insight into the possible range of results. *Sensitivity analysis* entails the determination of how rapidly the output of an analysis changes with respect to variations in the input. Meanwhile, it is also notable that sensitivity studies do not usually incorporate the error range or uncertainty of the input parameters—thus serving as a distinguishing element from uncertainty analyses.

12.1.3 Common Sources of Uncertainty in Public Health Endangerment Assessments

Inevitably, considerable uncertainty is inherent in the human risk assessment process; Box 12.1 identifies several major sources of uncertainty often associated with human health risk assessments. In particular, uncertainties arise due to the use of several assumptions and inferences necessary to complete a risk assessment. For instance, human health risk assessments usually involve extrapolations and inferences to predict the occurrence of adverse health effects under certain conditions of exposure to chemicals present in the environment. The extrapolations and inferences are typically based on knowledge of the adverse effects that occur under a different set of exposure conditions (e.g., different dose levels and/or species). As a consequence of these types of extrapolations and projections, there is considerable uncertainty in the resulting conclusions—due in part to the several assumptions that tend to be part of the overall evaluation process. Indeed, the dose-response analysis component of the chemical risk assessment process almost always raises questions about the likelihood that effects observed at the generally higher doses used in animal studies (or under conditions of workplace exposures) would actually or likely be observed at the generally lower doses expected in connection with environmental exposures; additionally, exposure assessment can involve an even broader range of uncertainties and related choice points—some associated with the fate and behavior of a chemical of interest in the environment or human tissue, others to data and uncertainties with respect to the metabolism, distribution, and ultimately fate of the chemical in the target population, etc. (NRC 2009).

Indeed, for most chemical substances for which there are insufficient data in humans, a major uncertainty in the evaluation of potential health effects to humans relates to the reliance on animal studies. Such applications involve the use of high exposure in animals to predict human response at lower exposure. Furthermore, this is often carried out in the absence of an understanding of how an agent causes the observed toxicological effects in the animals, and in the face of the varying results frequently obtained with different animal species under different exposure conditions. Even when there are human data, there is uncertainty about average response at lower exposures, and additionally, there is variability in individual response around this average. Still, risk assessment professionals frequently rely heavily on information generated from laboratory animal studies—i.e., despite the fact that biological differences among species and the use of high experimental doses often lead to significant uncertainties that are not easily resolved by traditional risk assessment methodologies.

On the whole, uncertainties are difficult to quantify, or at best, the quantification of uncertainty is itself uncertain. Thus, the risk levels generated in a risk assessment are useful only as a yardstick, and as a decision-making tool for the prioritization of problem situations—rather than to be construed as actual expected rates of disease, or adversarial impacts in exposed populations. For such reasons, it is used only as an estimate of risks, mostly based on current level of knowledge coupled with

several assumptions. Quantitative descriptions of uncertainty, which could take into account random and systematic sources of uncertainty in potency, exposure, intakes, etc. would usually help present the spectrum of possible true values of risk estimates, together with the probability (or likelihood) associated with each point in the spectrum.

Box 12.1 Major Sources of Uncertainty in Human Health Risk Assessments

- Uncertainty in health effects/toxicity data
  - Uncertainty in extrapolating from high dose to low dose
  - Uncertainty in extrapolating data from experimental animals to humans
  - Uncertainty due to differences between individuals
- Uncertainty in measuring or calculating exposure point concentrations
  - Uncertainty in transposing chemical source concentrations into exposure point concentrations
  - Uncertainty in assumptions used to model exposure point concentrations
- Uncertainty in calculating exposure dose
  - Uncertainty in source terms (i.e., chemical source sampling and monitoring data)
  - Uncertainty in estimating exposure dose using mathematical models

12.1.3.1 Archetypical Limitations and Uncertainties Often Encountered in Practice

In general, because of the various limitations and uncertainties often encountered in practice, the results of a risk assessment cannot be considered as an absolutely accurate determination of risks. In fact, this seems to present an almost contentious debate between various investigators—e.g., as eloquently articulated by Dr. Adam M. Finkel on one side of the argument, as follows: "If exposed to an identical concentration of a carcinogen, every human being would face a different level of risk, determined by his or her genetic, environmental, medical, and other uniquely individual characteristics. Various lines of evidence indicate that this susceptibility variable is distributed rather broadly in human populations, . . ., but cancer risk assessment at the EPA and elsewhere has always treated every (adult) human as identically susceptible. . ." (Finkel 2014). On the basis of the preceding argument, therefore, this has the potential for likely underestimation of risks. On the counter-argument side of the debate, however, other investigators do not appear to be in full agreement with the rationale offered by the opposition—and thus seem to disagree with (or at least minimize the impacts of) such assertions (e.g., Bogen 2014a, b).

Notwithstanding, commonly encountered limitations and uncertainties of considerable significance in relation to several components of the risk assessment process are enumerated below—each of which should perhaps be closely apprised for unique case-specific situations (see, e.g., Calabrese 1984; Clewell and Andersen 1985; Dourson and Stara 1983; USEPA 1989b).

- *Uncertainties in general extrapolations relevant to toxicity information*. Whereas some chemicals have been studied extensively under a variety of exposure conditions in several species (including humans), others may have only limited investigations done on them; this latter group will tend to have inherent limitations in toxicity data (arising for several reasons). Also, because data that specifically identify the hazards to humans as a result of their exposure to various chemicals of concern under the conditions of likely human exposure may not exist, it becomes necessary to infer such hazard effects by extrapolating from data obtained under different exposure conditions, usually in experimental animals. This introduces three major types of uncertainties—namely, that related to extrapolating from one species to another (i.e., uncertainties in inter-species extrapolation); those relating to extrapolation from a high-dose region curve to a low-dose region (i.e., uncertainties in intra-species extrapolation); and those related to extrapolating from one set of exposure conditions to another (i.e., uncertainties due to differences in exposure conditions).
- *Uncertainties from quantitative extrapolations and adjustments in dose-response evaluation*. Experimental studies to determine the likely carcinogenic effects due to low exposure levels often encountered in the environment generally are not feasible. This is because, such effects are not readily perceptible in the relatively short time frame over which it is usually possible to conduct such a study. Consequently, various mathematical models are used to extrapolate from the high doses used in animal studies to the doses likely to be encountered during exposure to ambient environmental concentrations. Extrapolating from a high dose (of animal studies) to a low dose (for human effects) introduces a level of uncertainty which could be significantly large, and which may have to be meticulously addressed. For instance, in human health risk assessments, no-observed-adverse-effect-levels (NOAELs) and cancer potency slope factors (SFs) from animal studies are usually divided by a factor of 10 to account for extrapolation from animals to humans, and by an additional factor of 10 to account for variability in human responses (see Chap. 10). Given the recognized differences among species in their responses to toxic insult, and between strains of the same species, it is apparent that additional uncertainties will likely be introduced when this type of quantitative extrapolations and adjustments are made in the dose-response evaluation.
- *Uncertainty associated with the toxicity of chemical mixtures*. The effects of combining two chemicals may be synergistic (effect when outcome of combining two chemicals is greater than the sum of the inputs), antagonistic (effect when the outcome is less than the sum of the two inputs), or under potentiation (i.e., when one chemical has no toxic effect but combined with another chemical

that is toxic, produces a much more toxic effect). Indeed, chemicals present in a mixture can interact to yield a new chemical; or one can interfere with the absorption, distribution, metabolism, or excretion of another. Notwithstanding all these possible scenarios, risk assessments often assume toxicity to be additive—resulting in a potentially significant source of uncertainty.

- *Limitations in model form*. Exposure scenarios, as well as fate and behavior models, usually can be a major contributor of uncertainty to risk assessments. Apart from general model imperfections, environmental and exposure models usually oversimplify reality—thus contributing one form of uncertainty or another. Also, the natural variability in environmental and exposure-related parameters causes variability in exposure factors, and therefore in exposure estimates developed on this basis. This, therefore, begs the question of how close to reality the model function and output are likely to be.
- *Consideration of ambient/'background' exposures*. For the most part, risk assessment methods used in practice tend to ignore background/ambient exposures; instead, the process considers only incremental risk estimates for the exposed populations. Consequently, such risk estimates do not address what constitutes the true health risks to the public—of which background or ambient exposures could be contributing in a very significant way. That said, it should also be acknowledged here that a good understanding of the role and influence of background levels of environmental chemicals can indeed involve several different typologies. Anyhow, to properly incorporate a consideration of background into environmental risk-based decision making, the multiple attributes of 'background' must be examined both individually and collectively.
- *Representativeness of sampling data*. Uncertainties may arise from random and systematic errors in the type of measurement and sampling techniques often used in environmental and exposure characterization activities. For instance, professional judgment (based on scientific assumptions) is frequently used for sampling design and also to make decisions on how to correct for data gaps—albeit this process has some inherent uncertainties associated with it.

In practice, very stage in the risk assessment process usually calls for a series of choices—each with the potential to influence, and in some cases determine, the outcome of the risk assessment. By and large, the data gaps and uncertainties inherent in the process might engender the need for a use of defaults and assumptions; in addition, utilization of alternative approaches with respect to each assumption may elicit the element of choice—and of course introduce its corresponding uncertainties (NRC 1994a, b, 2009).

12.1.4 The Need for Uncertainty and Variability Analyses

All risk estimates involve some degree of uncertainty and variability—especially because of the inability of the risk analyst to quantify all the requisite information

necessary to complete a credible study. Uncertainty analysis in particular should therefore become an integral part of all risk assessments, regardless of the scope or level of detail. Moreover, it is prudent and essential to the credibility of the risk assessment, to describe the relevant uncertainties in as great a detail as possible. But, as one strives to be more scientifically credible, it is also important not to attempt to infer levels of precision that clearly are not appropriate for quantitative risk assessments (Felter and Dourson 1998). After all, the acknowledgment of 'inexactness' is very much in line with a cautionary note that Aristotle is quoted to have sounded, once upon a time—that: "It is the mark of an instructed mind to rest satisfied with the degree of precision which the nature of the subject permits and not to seek an exactness where only an approximation of the truth is possible." Ultimately, the degree to which variability and uncertainty are addressed in a given study depends largely on the scope of the risk assessment and the resources available. For the study of variability, stochastic models are used as the more realistic representations of reality, rather than the use of deterministic models. In any case, as a guiding principle, the discussion of uncertainty and variability should, ideally, reflect the type and complexity of the risk assessment—with proportionate levels of effort dedicated to the risk assessment and the analysis or discussion of uncertainty and variability.

In the end, a number of factors—directly or indirectly related to uncertainties and variability—may undeniably cause a given analysis to either under-estimate or over-estimate true risks that are associated with a chemical exposure problem. For instance, it is always possible that a chemical whose toxic properties have not been thoroughly tested may be more toxic than originally believed or anticipated; a chemical not tested for carcinogenicity or teratogenicity may in fact display those effects; etc. Furthermore, an approach that limits an evaluation process to selected 'indicator chemicals' only may have some indeterminate (even if somehow insignificant) effects on the overall risk assessment exercise. Notwithstanding, a systematic and well-formulated presentation of uncertainty and variability analyses as part of the overall risk assessment process will generally help remove much of the concerns or doubts that could surround a given program.

12.1.4.1 General Degree and Scope of Uncertainty Analyses

Human health risk estimations that are customarily designed to potentially help decision makers reach the following feat in particular (IOM 2013):

- Evaluate alternative regulatory options;
- Assess how credible extreme risk estimates are, and how much to rely on them in decision making;
- Weigh the marginal decrease in risk against the effort made to reduce it;

- Clarify issues within a decision by using variant scenarios to characterize very 'different worlds'; and
- Identify regulatory solutions that are effective over a broad spectrum of scenarios—as may be applicable for some case-specific scenarios.

However, to assure credibility in the efforts involved, the characterization of all pertinent uncertainties becomes crucial; in this regard, the nature and sources of uncertainty are often seen as key determinants of the proper type of uncertainty analyses to be carried out. The appropriate extent or degree and scope of uncertainty analysis necessary for a given decision-making situation will generally depend on the types, source, and magnitude of the uncertainty as well as on the context of the decisions to be made—as, for example, the severity of the adverse effects and the timeframe within which a decision is needed.

At the end of the day, uncertainty analyses in human health risk estimates can help decision makers to weigh the marginal decrease in risk against the effort made to reduce such risks. In such efforts, decision makers need to understand—either quantitatively or qualitatively—the types and magnitude of the uncertainty that are present, in order to arrive at an informed decision. Meanwhile, it is noteworthy that the development and application of probabilistic techniques and Monte Carlo simulation methods to uncertainty analyses can add significant improvements to the overall risk estimation efforts.

12.1.4.2 The Uncertainty Analysis in Practice

Within any of the major steps of the human health risk assessment process, assumptions must be made due to a lack of absolute scientific knowledge. Some of the assumptions may be supported by reasonable amounts of scientific evidence, whiles others may not necessarily be supported to same level of confidence; regardless, every assumption likely introduces some degree of uncertainty into the risk assessment process. Traditionally, and especially in the regulatory realm of things, the risk assessment methodology tends to require that conservative assumptions be made throughout the risk assessment—at least to ensure that risks are not underestimated; on the other hand, when all of the conservative assumptions and approaches are combined, it is more likely that risk results/outcomes would be overestimated, rather than underestimated. Anyhow, insofar as possible, the assumptions that introduce the greatest amount of uncertainty in the risk assessment would tend be quantified and/or comprehensively discussed as part of the overall risk determination process; meanwhile, the assumptions for which there may not be enough information available to assign a numerical value to the uncertainty *per se* (and thus cannot be factored into the risk quantification/calculations) are typically discussed in qualitative terms. Ultimately, these uncertainties may also be properly incorporated into an overall risk management plan for pragmatic action.

Now, consider the following practical example discussion relating to the concepts offered in this chapter and elsewhere in the book; it is apparent that significant uncertainties exist in estimating dose-response relationships for potential carcinogens—due in part to experimental and epidemiologic variability, as well as uncertainty in extrapolating both from animals to humans, and from high to low doses. In exemplifying this type of case scenario, three major issues are identified as affecting the validity of toxicity assessments used to estimate potential excess lifetime cancer risks, namely: (1) the selection of a study (i.e., data set, animal species, matrix the constituent is administered in) upon which to base the calculations; (2) the conversion of the animal dose used to an equivalent human dose; and (3) the mathematical model used to extrapolate from experimental observations at high doses to the very low doses more likely to be encountered in the environment. *Study selection* involves the identification of a data set (experimental species and specific study) that provides sufficient, well-documented dose-response information to enable the derivation of a valid CSF. In this case, human data (e.g., from epidemiological studies) are preferable to animal data—albeit adequate human data sets are relatively rare. Therefore, it is often necessary to develop dose-response information from a laboratory species, ideally one that biologically resembles humans (e.g., with respect to metabolism, physiology, and pharmacokinetics), and where the route of administration is similar to the expected mode of human exposure (e.g., inhalation and ingestion). Next, assumptions for *dose conversions* involve standardized scaling factors to account for differences between humans and experimental animals with respect to lifespan, body size, breathing rates, and other physiological parameters. Moreover, evaluation of risks associated with one route of administration (e.g., inhalation) when tests in animals involve a different route (e.g., ingestion) requires additional assumptions with corresponding additional uncertainties. In regards to *high-to-low dose extrapolation*, it should be recognized that the concentration of constituents to which humans are potentially exposed in the environment is usually much lower than the levels used in the studies from which dose-response relationships are developed. Estimating potential health effects, therefore, requires the use of models that allow extrapolation of health effects from high experimental doses in animals to low environmental doses; these models are generally statistical in character and have uncertain biological basis—and thus the use of such models for dose extrapolation inevitably introduce uncertainty in the dose-response estimates. In addition, these models contain assumptions that may also introduce a large amount of additional uncertainty arising from a miscellany of sources. At the end of the day, these models typically would have been developed to err on the side of overestimating, rather than underestimating, potential health risks.

12.2 Characterization of Data Variability and Uncertainties

An uncertainty analysis consists of a process that translates uncertainties about models, variables and input data, as well as the random variability in measured parameters into uncertainties in output variables (Calabrese and Kostecki 1992; Finkel 1990; Iman and Helton 1988). The overall goal of an analysis of uncertainties is to provide decision-makers with the complete spectrum of information concerning the quality of an assessment—including the potential variability in the estimated parameters, the major data gaps, and the effect that such data gaps have on the accuracy and reasonableness of the estimates that are developed (Bogen 1990; Covello et al. 1987; Cox and Ricci 1992; Finkel and Evans 1987; Helton 1993; Hoffmann and Hammonds 1992; IOM 2013; Morgan and Henrion 1991; USEPA 1989a). Proper analysis and presentation of the uncertainties allow analysts or decision-makers to better evaluate the risk assessment results in the context of other factors being considered. This, in turn, will generally result in a more sound and open decision-making process.

The analysis of uncertainties will typically involve the following fundamental elements:

- Evaluation of uncertainties in the input of each of the relevant tasks;
- Propagation of input uncertainties through each task;
- Combination/convolution of uncertainties in the output from the various tasks; and
- Display and interpretation of the uncertainties in the final results.

On the whole, premium should be placed on a critical evaluation and presentation of all environmental, biological, and statistical uncertainties in the situation-specific assessment. Furthermore, it may be useful to carefully reexamine the quality of the studies used to support all conclusions, and to compare data across similar studies that are relevant to specific assessments. When appropriate, policy makers may employ plausible ranges associated with default exposure, as well as toxicological and other assumptions/policy positions; these may include, for instance, ranges of typical default values—such as the range of pulmonary ventilation rates (e.g., of 8–20 m^3/day), human body weight (e.g., of 10–60 or 70 kg), or ranges based on the use of low-dose extrapolation models (such as logit, probit, multistage, etc. models).

In the end, uncertainty analyses can have both qualitative and quantitative components/dimensions; accordingly, an uncertainty analysis can be performed qualitatively and/or quantitatively. But, whether qualitative or quantitative in nature, the analysis considers: uncertainties in every available database; uncertainties arising from assumptions in modeling; and the completeness of the analysis. Anyhow, the uncertainty analysis must be designed on a case-by-case basis—with the choice of uncertainty analysis protocol depending on the context of the decision, including the nature or type of uncertainty, and the factors that are considered in the

decision, as well as on the data that are available (IOM 2013). Indeed, most environmental problems will require the use of multiple approaches to uncertainty analysis; consequently, a mix of statistical analyses and expert judgments may be needed—albeit, in general, quantitative uncertainty analyses should probably be undertaken only when they are important and relevant to a given decision (e.g., such that at the end of the day, these quantitative uncertainty analyses would truly affect the environmental decision on hand). For that reason, if an environmental decision would stay the same for all states of information and analysis results, then it would not be worth conducting the identified type of analysis after all (IOM 2013).

12.2.1 Qualitative Analysis of Uncertainties

The qualitative analysis of uncertainties typically involves a determination of the general quality and reasonableness of the risk assessment data, parameters, and results. Qualitative analysis is usually most important to 'screening', 'preliminary', and 'intermediate' level types of assessments (USEPA 1989a).

As part of the qualitative analysis, the cause(s) of uncertainty is initially determined. The basic general cause of uncertainty is a lack of knowledge on the part of the analyst because of inadequate, or even nonexistent, experimental and operational data on key processes and parameters. The specific causes of uncertainty that are typically addressed here can be categorized as follows (USEPA 1989a, 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h):

- Measurement errors (resulting from measurement techniques employed in the study that could yield imprecise or biased measurements).
- Sampling errors (arising from the degree of representativeness of sampled data to actual population—e.g., small or unrepresentative samples).
- Aggregation errors (such as results from spatial and temporal approximations).
- Incomplete analysis (such as results from overlooking an important exposure scenario).
- Natural variability—e.g., in time, space, or activities.
- Model limitations (reflecting on how close to reality the models employed prove).
- Application and quality of generic or indirect empirical data.
- Professional/expert judgment (reflecting on the possible unreliability of scientific assumptions that may have been invoked or used—e.g., selection of an inappropriate model or surrogate data).

In general, once the causes of the uncertainties have been identified, the impact that these uncertainties have on the assessment results would then have to be determined. Insofar as possible, measures to minimize the impacts of such uncertainties on the results or final outcomes should be clearly expounded. Ultimately, the explicit presentation of the qualitative analysis results will transmit the requisite

level of confidence in the results to the decision-maker—facilitating the implementation of appropriate environmental and public health risk management actions.

12.2.2 Quantitative Analysis of Uncertainties

In addition to a qualitative analysis (as noted above), most detailed risk assessments may also require quantitative uncertainty analysis techniques to be used in chemical exposure studies. The quantitative analysis of uncertainties, often employed in detailed assessments, usually will proceed via sensitivity analysis and/or probabilistic analysis (e.g., Monte Carlo simulation techniques); the technique of choice normally depends on the availability of input data statistics. But, regardless of the technique of choice, the approach will generally allow for a deviation from the conservative and rather unrealistic approach of generating point estimates for risks, as has 'traditionally' been done in most risk assessment programs. Indeed, point estimates tend to confer a false sense of precision and population homogeneity—and thus may subsequently disguise the basis for rational decision-making. On the other hand, techniques such as Monte Carlo simulation provides a more complete description of risks—allowing risk managers and other stakeholders to appreciate/understand the level of protection offered by various risk management alternatives in an explicit manner. Ultimately, the Monte Carlo simulation approach helps the risk manager avoid making decisions based on implausible and unrealistic risk estimates.

In general, quantitative analysis of uncertainty becomes very important and necessary when prior risk screening calculations indicate a potential problem, or when risk control actions may result in excessively high costs, or when it is necessary to establish the relative importance of chemicals and exposure routes in a comparative analysis. Conversely, if estimated chemical intakes or risks are most obviously small and/or if the consequence of a 'wrong' prediction/decision based on the calculated risk is negligible, then perhaps quantitative analysis of uncertainty may neither be necessary nor a worthwhile effort.

12.2.2.1 Probabilistic Analysis: The Application of Monte Carlo Simulation Techniques

Various probabilistic analysis techniques can be employed/used to quantify uncertainties in risk assessment (e.g., Burmaster 1996; Finley and Paustenbach 1994; Finley et al. 1994a, b; Lee and Kissel 1995; Lee et al. 1995a, b; Macintosh et al. 1994; Power and McCarty 1996; Richardson 1996; Smith et al. 1992). The driving force behind the development and use of probabilistic risk assessment techniques has been the desire to more completely reveal the complexity in exposure conditions and toxicological responses that are present in the real world (Boyce 1998). Probabilistic risk analyses may indeed serve several purposes—including being

used to: propagate uncertainty in the estimate of exposure dose and risk; properly prioritize resources for risk reduction activities; and simulate stochastic variability among individuals in a population. Probabilistic analysis may surely be applied to the evaluation of risks in order that uncertainties are accounted for systematically.

In general, probabilistic analyses require data on the range and probability function (or distribution) of each model parameter. In fact, a central part of probabilistic risk analyses is the selection of probability distributions for the uncertain input variables (Haas 1997; Hamed and Bedient 1997a, b). Thus, it is usually recommended to undertake a formal selection among various distributional families, along with a formal statistical goodness-of-fit test, in order to obtain the most suitable family of statistical distributions appropriate for characterizing the case-specific data set. Ultimately, the favored probabilistic approach for assessing uncertainty is via 'Monte Carlo Simulation' (e.g., McKone 1994; McKone and Bogen 1991; Price et al. 1996; Smith 1994; Thompson et al. 1992). *Monte Carlo simulation* is a statistical technique by which a quantity is calculated repeatedly, using randomly selected/generated scenarios for each calculation cycle—and typically presenting the results in simple graphs and tables. The results from the simulation process approximate the full range of possible outcomes, and the likelihood of each.

The Monte Carlo simulation process involves assigning a joint probability distribution to the input variables; the procedure yields a concomitant distribution that is strictly a consequence of the assumed distributions of the model inputs and the assumed functional form of the model (Fig. 12.1). Meanwhile, it is noteworthy that several considerations may be important in the selection of appropriate probability distribution used to represent the relevant input parameters (Box 12.2) (Finley et al. 1994a; USEPA 1989a). In any event, unless specific information on the relationships between the relevant parameters is available, values for the required input parameters will normally be assumed to be independent.

Box 12.2 Important Considerations in the Selection of Appropriate Probability Distribution in a Monte Carlo Simulation

- A *uniform distribution* would be used to represent a factor/parameter when nothing is known about the factor except its finite range. The use of a uniform distribution assumes that all possible values within the range are equally likely.
- A *triangular distribution* would be used if the range of the parameter and its mode are known.
- A *Beta distribution* (scaled to the desired range) may be most appropriate if the parameter has a finite range of possible values and a smooth probability function is desired.
- A *Gamma, Log-Normal,* or *Weibull distribution* may be an appropriate choice if the parameter only assumes positive values. The Gamma

(continued)

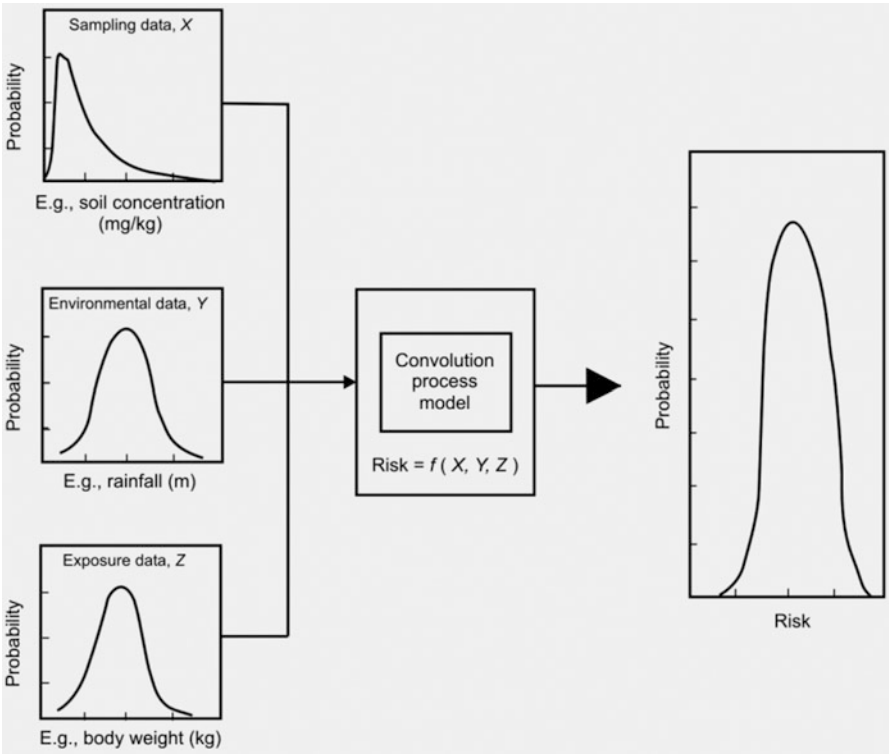

Fig. 12.1 Conceptual illustration of the Monte Carlo simulation procedure

Box 12.2 (continued)

distribution is probably the most flexible, especially because its probability function can assume a variety of shapes by varying its parameters, and it is mathematically tractable.

- A *Normal distribution* may be an appropriate choice if the parameter has an unrestricted range of possible values and is symmetrically distributed around its mode.

Monte Carlo simulations can indeed be used to develop numerical estimates of uncertainties that allow efficient ways to extend risk assessment methods to the estimation of both point values as well as distributional values of risks posed by chemical exposure problems. In using Monte Carlo techniques, most or all input variables to the risk assessment models become random variables with known or estimated probability density functions (pdfs). Within this framework, a variable can take on a range of values with a known probability. In general, when Monte Carlo Simulation is applied to risk assessment, the risk presentation appears as

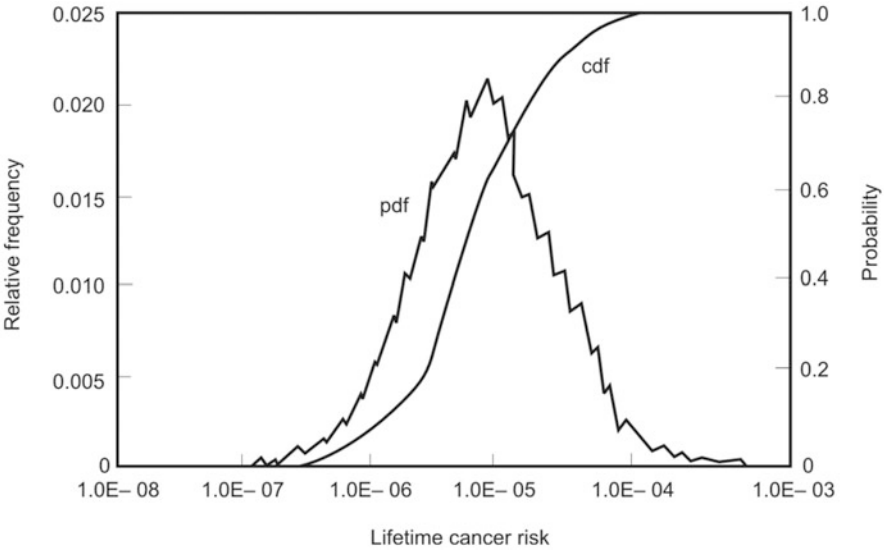

Fig. 12.2 An illustrative sketch of a plot from a Monte Carlo simulation analysis (showing probability density function [pdf] and cumulative distribution function [cdf] for lifetime cancer risks from a contaminated site)

frequency or probability distribution graphs—as illustrated by the sketch shown in Fig. 12.2—from which the mean, median, variance, and/or percentile levels/values can be extracted.

12.2.3 Presentation Formats for Uncertainty in Risk Estimates

The most widely used 'formal language' of uncertainty in risk estimates is probability (IOM 2013; Morgan 2009)—albeit it is generally recognized that 'probabilities are notoriously difficult to communicate effectively to lay audiences' (Spiegelhalter et al. 2011); yet still, these layperson groups are likely to form a significant portion of the stakeholder pool for the types of programs envisaged for most public health risk assessment/management situations. Alternatively, probabilistic information, and the uncertainties associated with those probabilities, can usually be communicated using numeric, verbal, or graphic formats—forms likely to be more amenable to effective risk communication to broad-spectrum audience. At least for the aforementioned reasons, careful consideration should generally be given to the most appropriate approach for the circumstances being evaluated (Fagerlin et al. 2007; Lipkus 2007; Nelson et al. 2009; Spiegelhalter et al. 2011; Visschers et al. 2009). In any event, regardless of the format in which the uncertainty is presented, it is important to bound the uncertainty and to describe the effect

it might have on the ultimate decision; presenting the results/outcomes via sensitivity analyses scenarios is one way to provide some boundaries on the effects of those uncertainties, and to educate stakeholders about how those uncertainties might affect a given decision (IOM 2013).

12.2.3.1 Numeric Vs. Verbal/'Linguistic' Vs. Graphical Presentations of Uncertainty

Risk probabilities and associated uncertainties may typically be presented in various formats—most commonly as numeric values, 'verbal statements', and/or graphically. Somehow, it is believed that numeric presentations of probabilistic information can eventually (even if conditionally) lead to better perceptions of risk than verbal and graphic formats (Budescu et al. 2009; IOM 2013).

Numeric presentations of probabilistic information—such as in terms of percentages and frequencies—often become the preferred approach for most analysts. Percentage and frequency formats have indeed been found to be (conditionally) more effective than most other formats for a number of circumstances because they more readily allow the stakeholder pool to conduct simple mathematical operations (such as comparisons) on risk probabilities (Cuite et al. 2008). Among the key disadvantages of numeric presentations are that, they are only useful if the primary stakeholders being communicated with are capable of interpreting the numeric information presented; also, they may not particularly hold certain groups of people's attention as well as verbal and graphic presentations (Krupnick et al. 2006; IOM 2013; Lipkus 2007).

Verbal presentations of risk—for example, messages containing words such as 'likely' or 'unlikely'—can be used as calibrations of numeric risk; such representations may indeed do a better job of capturing people's attention than numeric presentations, and they are also effective for portraying 'directionality' (IOM 2013). Furthermore, verbal expressions of uncertainty can be better adapted to the level of understanding of an individual or group than can numeric and graphic presentations (IOM 2013; Kloprogge et al. 2007). A major weakness of 'verbal' or 'linguistic' presentations of risk is that some studies have shown that the probabilities attributed to words such as 'likely' or 'very likely' varies among individuals—and indeed can even vary for a single individual depending on the scenario being presented (see, e.g., Erev and Cohen 1990; Morgan 1998; Morgan 2003; Wallsten and Budescu 1995; Wallsten et al. 1986). Thus, qualitative descriptions of probability—that is, those that include a description or definition for a category of certainty—are sometimes used instead of such subjective calibrations as 'very likely' or 'unlikely' which are open for individual interpretations, etc. (Budescu et al. 2009; IARC 2006; IPCC 2001, 2007; Moss and Schneider 2000; Smithson et al. 2011).

Graphical displays of probabilistic information—such as bar charts, pie charts, and line graphs—can usually summarize more information than other presentation modes, as well as can capture and hold people's attention, and can show patterns

and 'whole-to-part' relationships (Budescu et al. 1988; IOM 2013; Spiegelhalter et al. 2011). Furthermore, uncertainties about the outcomes of an analysis can also be depicted using graphical displays, such as bar charts, pie charts, probability density functions, cumulative density functions, and box-and-whisker plots—among others. For instance, probability density functions can be a sensitive indicator of variations in probability density, and thus their use may be advantageous when it is important to emphasize small variations; on the other hand, this sensitivity may sometimes be a disadvantage—in that small variations attributed to random sampling may be present as 'noise', and are of no intrinsic interest, etc. Cumulative distribution functions (CDFs) seem to have the advantage of not showing as much small variation noise as a probability density function does, so that the shape of the distribution may appear much smoother—albeit this has its own shortcomings as a tool for a broad stakeholder base (Ibrekk and Morgan 1987; IOM 2013). Box-and-whisker plots are effective in displaying summary statistics (medians, ranges, fractiles), but they provide no information about the shape of the distribution except for the presence of asymmetry in the distribution (Krupnick et al. 2006). Anyway, despite their advantages, graphic displays do not always explicitly describe conclusions—and they can indeed require more effort to extract information, particularly for people who are not familiar with the mode of presentation or who lack skills in interpreting graphs or in cases where the graphic presents complex data (Boduroglu and Shah 2009; IOM 2013; Kloprogge et al. 2007; Lipkus 2007; Shah and Freedman 2009; Slovic and Monahan 1995; Slovic et al. 2000; Spiegelhalter et al. 2011; Stone et al. 1997).

In the final analysis, perhaps using a mix of verbal terms, numerical values, and graphical displays to communicate uncertainty might portray a relatively better overall picture.

12.3 Presenting and Managing Uncertain Risks: The Role of Sensitivity Analyses

Inevitably, some degree of uncertainties remains in quantitative risk estimates in virtually all fields of applied risk analysis. A carefully executed analysis of uncertainties therefore plays a very important role in all risk assessments. On the other hand, either or both of a comprehensive qualitative analysis and a rigorous quantitative analysis of uncertainties will be of little value if the results of such analysis are not clearly presented for effective use in the decision-making process. To facilitate the design of an effectual process, a number of methods of approach have been suggested by some investigators (e.g., Cox and Ricci—see, Paustenbach 1988) for presenting risk analysis results to decision-makers, including the following:

- Risk assessment results should be presented in a sufficiently disaggregated form (to show risks for different subgroups) so that key uncertainties and heterogeneities are not lost in the aggregation.
- Confidence bands around the predictions of statistical models can be useful, but uncertainties about the assumptions of the model itself should also be presented.
- Both individual (e.g., the typical and most threatened individuals in a population) and population/group risks should be presented, so that the equity of the distribution of individual risks in the population can be appreciated and taken into account.
- Any uncertainties, heterogeneities, or correlations across individual risks should be identified.
- Population risks can be described at the 'micro' level (namely, in terms of frequency distribution of individual risks), and/or at the 'macro' level (namely, by using decision-analytic models, in terms of attributes such as equivalent number of life-years).

On the whole, uncertainty is typically expressed in terms of the probability or likelihood of an event, and can indeed be presented numerically, verbally, and/or graphically—with each approach having its unique advantages and disadvantages (IOM 2013). It is noteworthy that, the uncertainty analysis can also be achieved via sensitivity analyses for key assumptions.

Sensitivity analysis is generally defined as the assessment of the impact of changes in input values on model outputs. Often a useful adjunct to the traditional uncertainty analysis, sensitivity analysis is comprised of a process that examines the relative change or response of output variables caused by variation of the input variables and parameters (Calabrese and Kostecki 1992; Iman and Helton 1988; USEPA 1992a, b, c, d, e, 1997a, b, c, d, e, f, g, h). It is indeed a technique that tests the sensitivity of an output variable to the possible variation in the input variables of a given model. Accordingly, the process serves to identify the sensitivity of the calculated result vis-à-vis the various input assumptions—and thus identify key uncertainties, as well as help bracket potential risks so that policy-makers can make more informed decisions or choices.

Typically, the performance of sensitivity testing requires data on the range of values for each relevant model parameter. The intent of sensitivity analysis is then to identify the influential input variables, and to develop bounds on the model output. When computing the sensitivity with respect to a given input variable, all other input variables are generally held fixed at their 'nominal' values. By identifying the influential or critical input variables, more resources can then be directed to reduce their uncertainties—and thence reduce the output uncertainty. Thus, as an example, the main purpose of sensitivity analyses in an exposure characterization would be to determine which variables in the applicable model equations, as well as the specific pathways or scenarios, would likely affect the consequential exposure estimates the most. These techniques can also be used to assess key sources of variability and uncertainty for the purpose of prioritizing additional data collection and/or research efforts.

In the end, notwithstanding the added value of sensitivity analyses, several factors may still contribute to the over- or under-estimation of risks. For example, in human health risk assessments, some factors will invariably underestimate health impacts associated with the chemicals evaluated in the assessment. These may include: lack of potency data for some carcinogenic chemicals; risk contributions from compounds produced as transformation byproducts, but that are not quantified; and the fact that all risks are assumed to be additive, although certain combinations of exposure may potentially have synergistic effects. Conversely, another set of factors would invariably cause the process to overestimate risks. These may include the fact that: many unit risk and potency factors are often considered plausible upper-bound estimates of carcinogenic potency, when indeed the true potency of the chemical could be considerably lower; exposure estimates are often very conservative; and possible antagonistic effects, for chemicals whose combined presence reduce toxic impacts, are not accounted for properly.

12.4 Coming to Terms with Uncertainty and Variability Issues in Risk Assessment

Uncertainty seems foremost among the recurring themes in risk assessment; in quantitative assessments, *uncertainty* relates to lack of information, incomplete information, or incorrect information (NRC 2009). Uncertainty in a risk assessment depends on the quantity, quality, and relevance of data—as well as on the reliability and relevance of models and inferences used to fill data gaps; for example, the quantity, quality, and relevance of data on dietary habits and a pesticide's fate and transport will affect the uncertainty of parameter values used to assess population variability in the consumption of the pesticide in food and drinking water (NRC 2009). As to variability, it can be said that there are important variations among individuals in a population with respect to susceptibility and exposure.

Characterizing uncertainty and variability is crucial to the human health risk assessment process; among other things, the analytical protocols used in the risk determination efforts must engage the best available science in the presence of uncertainties, as well as often difficult-to-characterize variability—in order to properly inform risk management and related decisions (NRC 2009). Indeed, proper characterization of each stage in the risk assessment process—starting from environmental release or hazard realization through to chemical exposure, and onto the recognition of health effect(s)—invariably poses significant analytic challenges that cannot quite be ignored *per se*. Thus, each component of a risk assessment should strive to include uncertainty and variability considerations—preferably in an explicitly characterized manner. Meanwhile, it is noteworthy that many of the statistical techniques and general concepts used in relation to uncertainty analysis are also applicable to variability analysis; however, the key difference between uncertainty analysis and variability analysis relates to the fact that

variability can only be better characterized, not reduced—and thus it often must be addressed with strategies somewhat different from those used to address uncertainty (NRC 2009).

In the end, the following guiding principles are recommended in the efforts at addressing the likely wide-ranging issues pertaining to uncertainty and variability in risk assessments (NRC 2007a, b, 2009; IOM 2013):

1. Risk assessments should provide a quantitative, or at least qualitative, description of uncertainty and variability consistent with available data—recognizing that the information required or necessary to carry out detailed uncertainty analyses may not be available in many situations.
2. In addition to characterizing the broader population group at risk, special attention should be directed to vulnerable individuals and subpopulations that may be particularly susceptible or relatively more highly exposed.
3. The depth, extent, and detail of the uncertainty and variability analyses should be commensurate with the importance and nature of the decision to be informed by the risk assessment, and with what is considered as the valued assets in a decision. This may best be achieved by early engagement of risk assessors/analysts, risk managers, and other stakeholders with respect to the nature and objectives of the risk assessment, as well as the terms of reference—all of which must be clearly defined upfront.
4. The risk assessment should systematically compile or otherwise characterize the types, sources, extent, and magnitude of variability and substantial uncertainties associated with the overall assessment. To the extent feasible, there should be homologous treatment of uncertainties among the different components of a risk assessment, as well as among different policy options being compared.
5. To maximize public understanding of, and participation in, risk-related decision-making, a risk assessment should endeavor to explain the basis and results of the uncertainty analysis with sufficient clarity to be understood by the general (layperson) public and decision-makers.
6. Uncertainty and variability should preferably be kept conceptually separate in the risk characterization.
7. The uncertainty assessment should not be a significant source of delay in the release of a given project's risk assessment.

When all is said and done, depending on the risk management options being considered, a quantitative treatment of uncertainty and variability may be needed to differentiate among the options—in order to arrive at well-informed decisions. Uncertainty analysis is indeed important for both data-rich and data-poor situations—albeit confidence in the analysis will vary according to the amount of information available (NRC 2009).

In closing, it must be accentuated here that the results of deterministic risk assessments should be interpreted with caution, and never construed as absolute measures of risk—especially when uncertainty and variability factors may not have been properly taken into account. Even so, the resultant point estimates of risk so-generated may still be useful in a qualitative sense for the ranking of different

public health risk management programs or issues. At any rate, probabilistic methods must be encouraged as the logical evolution of the risk assessment process—and perhaps this should be accompanied by the development of risk management methods that can utilize the richness of information provided by Monte Carlo assessments and other similar techniques (Zemba et al. 1996). In fact, it is believed that, the danger of mischaracterizing high-end, central tendency, and surely other statistical exposure levels can only be properly alleviated via the development and utilization of full probabilistic analyses.