Chapter 8
Interpreting Uncertainty for Human Health Risk Assessment

What's Covered in Chapter 8:

This section discusses interpreting uncertainties associated with the risk assessment. The discussion of uncertainties in Section 8.1 and 8.2 was adopted from the *1996 Risk Assessment Support to the Development of Technical Standards for Emissions from Combustion Units Burning Hazardous Waste*.

> ***PLEASE NOTE***: for the purposes of this guidance, "we" refers to the U.S. EPA OSW.
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> The HHRAP is written for the benefit of a varied audience, including risk assessors, regulators, risk managers, and community relations personnel. However, the "you" to which we speak in this chapter is the performer of a risk assessment: the person (or persons) who will actually put the recommended methods into practice.

8.1 UNCERTAINTY AND LIMITATIONS OF THE RISK ASSESSMENT PROCESS

Uncertainty can be introduced into a health risk assessment at every step of the process outlined in this document. Uncertainty occurs because risk assessment is a complex process, requiring the integration of the following:

- Release of pollutants into the environment
- Fate and transport of pollutants, in a variety of different and variable environments, by processes that are often poorly understood or too complex to quantify accurately

- Potential for adverse health effects in humans, as extrapolated from animal studies
- Probability of adverse effects in a human population that is highly variable genetically, and in age, activity level, and lifestyle

Uncertainty is inherent in the process even when using the most accurate data and the most sophisticated models. The method we recommend in the HHRAP relies on a combination of point values—some protective and some typical—yielding a point estimate of exposure and risk that falls at an unknown percentile of the full distributions of exposure and risk. For this reason, the degree of conservatism in risk estimates cannot be known. Therefore, you need a formal uncertainty analysis to determine the degree of conservatism. Section 8.2 discusses the types of uncertainty and the areas in which uncertainty can be introduced into an assessment. The remaining Sections discuss methods for qualitatively and quantitatively addressing uncertainty in risk assessments.

It should also be noted, variability is often used interchangeably with the term "uncertainty," but this is not strictly correct. "Variability" may be tied to variations in physical and biological processes. Variability can't be reduced with additional research or information, although it may be known with greater certainty (for example, the age distribution of a population may be known and represented by the mean age and its standard deviation). "Uncertainty" is a description of the imperfect knowledge of the true value of a particular variable, or its real variability in an individual or a group.

In general, uncertainty is reducible by additional information-gathering or analysis activities (that is, better data or better models), whereas real variability won't change (although it may be more accurately known) as a result of better or more extensive measurements (Hattis and Burmaster 1994).

8.2 TYPES OF UNCERTAINTY

Finkel (1990) and U.S. EPA (1999f) classified all uncertainty into four types:

1. variable uncertainty,
2. model uncertainty,
3. decision-rule uncertainty, and
4. variability.

Variable uncertainty and model uncertainty are generally recognized by risk assessors as major sources of uncertainty. Variable uncertainty occurs when variables appearing in equations cannot be measured precisely or accurately, because of either (1) equipment limitations, or (2) spatial or temporal variances between the quantities being measured. Random, or sample, errors are common sources of variable uncertainty that are especially critical for small sample sizes. It is more difficult to recognize nonrandom, or systematic, errors that result from the basis for sampling, experimental design, or choice of assumptions.

Model uncertainty is associated with all models used in all phases of a risk assessment, including:

- animal models used as surrogates for testing human carcinogenicity,
- the dose-response models used in extrapolations, and
- the computer models used to predict the fate and transport of chemicals in the environment.

Using rodents as surrogates for humans introduces uncertainty into the risk factor because of the considerable interspecies variability in sensitivity. Computer models are simplifications of reality, requiring exclusion of some variables that influence predictions but cannot be included in models because of (1) increased complexity, or (2) a lack of data for these variables. The importance of excluded variables is generally considered on a case-by-case basis. A specific variable may be important, in terms of its impacts on uncertainty, in some instances and not in others. A similar problem can occur when a model that is applicable under average conditions is used for a case in which conditions differ from the average. Finally, choosing the correct model form is often difficult, because conflicting theories appear to explain a phenomenon equally well.

The models we recommend in the HHRAP were selected based on scientific policy. We selected the air dispersion and deposition model, and the indirect exposure models, because they provide the information you need to conduct indirect assessments, and we consider them state-of-the-science. ISCST3—the air dispersion model we recommend—has not been widely applied in its present form. Few data are available on atmospheric deposition rates for chemicals other than criteria pollutants, thereby making it difficult to select input variables related to deposition, or validate modeled deposition rates. Long-range transport of pollutants into and out of the study areas wasn't modeled, resulting in an underestimation of risk attributable to each facility.

In addition to air dispersion modeling, using other fate and transport models recommended by this guidance can also result in some uncertainty. For example, the models which estimate COPC concentrations in waterbodies may be particularly protective for waterbodies located in estuarine environments with tidal influence. Because tidal influence is not considered in the models presented in Chapter 5, the resulting dilution of COPC concentrations in water and sediments likely caused by tidal influence won't be considered in the risk assessment. Thus, the risk assessment results will likely be more protective for tidally influenced waterbodies than for those waterbodies that aren't tidally influenced. We recommend that permitting decisions based on risk estimates for estuarine environments consider this uncertainty. The delineation of this uncertainty may be one area that could be addressed in a more refined site-specific risk assessment, if warranted.

Decision-rule uncertainty is probably of greatest concern to risk managers. This type of uncertainty arises, for example, out of the need to balance different social concerns when determining an acceptable level of risk. The uncertainty associated with risk analysis influences many policy and risk management decisions. Possibly the most important aspect for the risk estimates is the selection of constituents to be assessed. Constituents that are identified using the process provided in this document will include compounds that have the potential to pose the greatest risk to human health through indirect exposure routes. For example, many PICs are highly lipophilic and tend to bioaccumulate in the food chain, thereby presenting a potentially high risk through the consumption of contaminated food.

A second area of decision-rule uncertainty includes the use of standard Agency default values in the analysis. These include inhalation rates, body weight, and lifespan, which are standard default values used in most Agency risk assessments. Inhalation rate is highly correlated to body weight for adults. Using a single point estimate for these variables instead of a joint probability distribution ignores a variability that may influence the results by a factor of up to two or three.

A third area of decision-rule uncertainty is the use of Agency-verified cancer *SFs*, *RfDs*, and *RfCs*. These health benchmarks are used as single-point estimates throughout the analysis, and uncertainty and variability are both associated with them. U.S. EPA has developed, however, a process for setting verified health benchmark values to be used in all Agency risk assessments. This process is used to account for much of the uncertainty and variability associated with the health benchmarks. With the exception of the dioxin toxicity equivalency methodology, health benchmarks which can be found on

IRIS, have been verified through Agency work groups. Estimating the uncertainty in using Agnecy-verified health benchmarks or the dioxin toxicity equivalency methodology is beyond the scope of the HHRAP.

8.3 QUALITATIVE ESTIMATES OF UNCERTAINTY

Often, sources of uncertainty in a risk assessment can be identified but not quantified. For example, this can occur when you know (or suspect) a factor to vary, but have no data (e.g., presence of COPCs without toxicity data, amount of time that people at a specific site spend outdoors). In such cases, default data may be available that can be useful in estimating a possible range of values. Uncertainty also often arises out of a complete lack of data. A process may be so poorly understood that you can't quantify the uncertainty with any confidence. In addition, some sources of uncertainty (such as uncertainty in theories used to deduce models) are inherent qualifications reflecting subjective modes of confidence rather than probabilistic arguments. When you can only present the uncertainty qualitatively, you might consider the possible direction and orders of magnitude of the potential error.

8.4 QUANTITATIVE ESTIMATES OF UNCERTAINTY

It's also possible to use knowledge of experimental or measurement errors to introduce a degree of quantitative information into a qualitative presentation of uncertainty. For example, standard laboratory procedures or field sampling methods may have a known error level that you can use to quantify uncertainty. In many cases, it's possible to express the uncertainty associated with particular variable values or estimated risks quantitatively, and further evaluate them with variations of sensitivity analyses. Finkel (1990) identified a six-step process for producing a quantitative uncertainty estimate:

1. Define the measure of risk (such as deaths, life-years lost, maximum individual risk (MIR), or population above an "unacceptable" level of risk). More than one measure of risk may result from a particular risk assessment: however, the uncertainty may be quantified or reached individually.

2. Specify "risk equations" that present mathematical relationships that express the risk measure in terms of its components. This step is used to identify the important variables in the risk estimation process.

3. Generate an uncertainty distribution for each variable or equation component. These uncertainty distributions may be generated by using analogy, statistical inference techniques, expert opinion, or a combination of these.

4. Combine the individual distributions into a composite uncertainty distribution.

5. Recalibrate the uncertainty distributions. Inferential analysis could be used to "tighten" or "broaden" particular distributions to account for dependencies among the variables and to truncate the distributions to exclude extreme values.

6. Summarize the output clearly, highlighting the important risk management implications. Address specific critical factors.
   - Implication of supporting a point estimate produced without considering uncertainty
   - Balance of the costs of under- or over-estimating risks
   - Unresolved scientific controversies, and their implications for research

When you need a detailed quantitative treatment of uncertainty, statistical methods are generally considered the most appropriate. We describe two possible approaches to a statistical treatment of uncertainty with regard to variable values here, though other methods are certainly available. The methods described here were used in this analysis where appropriate.

The first approach is to use an appropriate statistic to express all variables for which uncertainty is a major concern. For example, if a value comes from a sample (such as yearly emissions from a stack), the mean and standard deviation may both be presented. If the sample size is very small, it may be appropriate to

- give the range of sample values and use a midpoint as a best estimate in the model, or
- use the smallest and largest measured value to obtain two estimates that bound the expected true value.

Selecting the appropriate statistic depends on the amount of data available and the degree of detail you need. It's possble to propagate uncertainties by using analytical or numerical methods.

A second approach is to use the probability distributions of major variables to propagate variable value uncertainties through the equations you use in the risk assessment. You then develop a probability distribution of expected values for each variable value. These probability distributions are typically

expressed as either probability density functions (*PDF*) or cumulative probability density functions (*CPF*). The *PDF* presents the relative probability for discrete variable values, whereas the *CPF* presents the cumulative probability that a value is less than or equal to a specific value.

A composite uncertainty distribution is created by combining the individual distributions with the equations used to calculate the probability of particular adverse health effects and points. In Monte Carlo simulations, a computer program is used to repeatedly solve the model equations, under different selections of variable values, to calculate a distribution of exposure (or risk) values. Each time the equations are calculated, values are randomly sampled from the specified distributions for each variable. The end result is a distribution of exposure (or risk). These can again be expressed as *PDF*s or, more appropriately, as *CPF*s. The distribution enables you to choose the value corresponding to the appropriate percentile in the overall distribution. For example, you could select an exposure level or risk level that corresponds to the 95th percentile of the overall risk distribution rather than a point estimate of risk that is based on the 95th percentile values for each variable. For more information on how to conduct a quantitative uncertainty analysis, we refer you to Risk Assessment Guidance for Superfund, Volume III: Part A (Process for Conducting Probabilistic Risk Assessment), which is located at the web address www.epa.gov/oswer/riskassessment/rags3a/index.htm.

8.5 RISK ASSESSMENT UNCERTAINTY DISCUSSION

The science of risk assessment is evolving. Where the science-base is incomplete and uncertainties exist, science policy assumptions must me made. It is important for risk assessments to fully explain the areas of uncertainty in the assessments and to identify the key assumptions used in conducting the assessments. Toward that end, one option is to add a table at the end of each section (e.g., stack emissions, air modeling, exposure assessment, toxicity evaluation, risk characterization) that lists the key assumptions in that section, the rationale for those assumptions, their effect on estimates of risk (overestimation, underestimation, neutral), and the magnitude of the effect (high, medium, low). For example, it could explain that using a particular input variable, such as exit gas temperature, will under- or overestimate chronic emissions, and the resulting risks and hazards, by a factor of (x). These tables could be used to evaluate the extent to which you used public health-protective assumptions in the risk assessment. They could also help determine the nature of the uncertainty analysis to be performed. The assumptions listed

in the risk characterization section, which synthesizes the data outputs from the exposure and toxicity analyses, might include the most significant assumptions from each of the previous sections.

Within the HHRAP, we've identified uncertainties and limitations within the discussion of specific technical issues (e.g., TOE, estimates of emission rates, COPC selection process, quantifying non-detects) as they are presented in their respective sections. We present the limitations associated with parameter values and inputs to equations in Appendices A, B, and C, respectively.

As an example discussion, the following summarizes some of the uncertainty involved in the air dispersion modeling component of the risk assessment process.

Although dispersion modeling is a valuable tool for estimating concentration and deposition impacts, it has many limitations. The accuracy of the models is limited by

- the ability of the model algorithms to depict atmospheric transport and dispersion of contaminants, and
- the accuracy and validity of the input data.

For example, most refined models require input of representative meteorological data from a single measuring station. In reality, a release will encounter highly variable meteorological conditions that are constantly changing as it moves downwind. U.S. EPA's *Guideline on Air Quality Models—Revised* (U.S. EPA 1986b, 1993b; Title 51 CFR Appendix W) describes two types of model uncertainty. Inherent uncertainty involves deviations in concentrations that occur even if all of the model input is accurate. Reducible uncertainty is associated with the model and the uncertain input values that will affect the results. Although it is important to accurately represent actual conditions by selecting the right model, and using accurate and representative input data, all model results are subject to uncertainty. Nevertheless, models are generally considered reasonably reliable in estimating the magnitude of highest concentrations resulting from a release, although they may not necessarily be time-and space-specific (Title 51 CFR Appendix W). When applied properly, air dispersion models are typically accurate to ± 10 to 40 percent and can be used to yield a "best estimate" of air concentrations (Title 51 CFR Appendix W).

As mentioned earlier, uncertainties specific to other technical components of the risk assessment process (e.g., TOE, quantification of non-detects) are further described in their respective chapters or sections of

this guidance. For more information on Agency policy and guidelines regarding uncertainty in risk assessments, please see the U.S. EPA Science Policy Council's *Risk Characterization Handbook* (U.S. EPA 2000f, available at http://www.epa.gov/osa/spc/pdfs/rchandbk.pdf).