
Friday
November 23, 1984

Part VIII

**Environmental
Protection Agency**

Proposed Guidelines for Exposure
Assessment; Request for Comments

003726

ENVIRONMENTAL PROTECTION AGENCY

[FRL-2706-5]

Proposed Guidelines for Exposure Assessment

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed Guidelines for Exposure Assessment and Request for Comments.

SUMMARY: The U.S. Environmental Protection Agency is proposing Guidelines for Exposure Assessment (Guidelines). These Guidelines are proposed for use within the policy and procedural framework provided by the various statutes which EPA administers to guide Agency analysis of exposure data. We solicit public comment and will take public comment into account in revising these Guidelines. These Guidelines will be reviewed by the Science Advisory Board in meetings now tentatively scheduled for April 1985.

These proposed Guidelines were developed as part of a broad guidelines development program under the auspices of the Office of Health and Environmental Assessment (OHEA), located in the Agency's Office of Research and Development. Consonant with the role of OHEA's Exposure Assessment Group (EAG) as the Agency's senior health committee for exposure assessment, the Guidelines were developed by an Agency-wide working group chaired by the Director of EAG.

DATE: Comments must be postmarked by January 22, 1985.

ADDRESSES: Comments may be mailed or delivered to: Dr. James W. Falco, Exposure Assessment Group (RD-689), Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, 401 M Street S.W., Washington, DC 20460.

FOR FURTHER INFORMATION CONTACT: Dr. James W. Falco, Telephone: 202-475-8909.

SUPPLEMENTARY INFORMATION: Preliminary drafts of these Guidelines were sent out for review to 15 scientists and engineers in the field of exposure assessment within government, universities in the United States and abroad, and the private sector. Comments received from these reviews, generally favorable, were taken into account in developing the Guidelines proposed here.

In addition, as a result of the reviews, four areas requiring further research were identified as follows:

(1) Development of Mathematical Model Selection Criteria.

A large number of mathematical models are used to estimate a wide variety of parameters needed for estimating exposures. Guidance in the form of selection criteria are needed to ensure that the most appropriate mathematical model is used for each exposure parameter estimate.

(2) Development of Guidance for Analysis of Metabolism Data.

Guidance is needed to provide appropriate consideration of metabolism data in the calculation of whole body dose and in the extrapolation of whole organism dose from one species to another.

(3) Definition of the Relationship Between Exposure Assessment and Epidemiology.

Guidance is needed to ensure that pertinent parameters of exposure are measured in prospective epidemiologic studies. Methods providing the best estimates of exposure for retrospective and historical epidemiologic studies must be defined.

(4) Development of Methods to Relate Exposures Measured by Personal Monitoring to Source Contributions.

Guidance is needed to establish methods to relate exposures as measured by personal monitoring to controllable sources and to discriminate among possible sources and between background and anthropogenic sources. It is the Agency's intent to revise the Guidelines periodically to incorporate the results obtained in the four research areas defined above as they become available.

In addition to the publication of the Guidelines, the Agency also will provide technical support documents that contain detailed technical information needed to implement the Guidelines. Two of these technical reports entitled "Development of Statistical Distribution or Ranges of Standard Factors Used in Exposure Assessments" and "Methodology for Characterization of Uncertainty in Exposure Assessments" are currently available. Technical reports for the four new guideline areas described above will be available at the time of publication of the corresponding guideline section. These technical support documents will be revised periodically to reflect improvements in exposure assessment methods and new information or experience.

Support documents used in the preparation of these Guidelines as well as comments received are available for inspection and copying at the Public Information Reference Unit (202-382-5926), EPA Headquarters Library, 401 M

Street S.W., Washington, DC, between the hours of 8:00 a.m. and 4:30 p.m.

Dated: November 9, 1984.

William D. Ruckelshaus,
Administrator.

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I. Introduction

These Guidelines provide the Agency with a general approach and framework for carrying out human or nonhuman exposure assessments for specified pollutants. The Guidelines have been developed to assist future assessment activities and encourage improvement in those EPA programs that require, or could benefit from the use of exposure assessments. The Guidelines are procedural. They should be followed to the extent possible in instances where exposure assessment is a required element in the regulatory process or where exposure assessments are carried out on a discretionary basis by EPA management to support regulatory or programmatic decisions.

This document, by laying out a set of questions to be considered in carrying out an exposure assessment, should help avoid inadvertent mistakes of omission. EPA recognizes that gaps in data will be common, but the Guidelines will nevertheless serve to assist in organizing the data that are available, including any new data developed as part of the exposure assessment. It is understood that exposure assessments may be performed at many different levels of detail depending on the scope of the assessment.

These Guidelines should also promote consistency among various exposure assessment activities that are carried out by the Agency. Consistency with respect to common physical, chemical, and biological parameters, with respect to assumptions about typical exposure

situations, and with respect to the characterization of uncertainty of estimates, will enhance the comparability of results and enable the Agency to improve the state-of-the-art of exposure assessment over time through the sharing of common data and experiences.

It is recognized that the main objective of an exposure assessment is to provide reliable data and/or estimates for a risk assessment. Since a risk assessment requires the coupling of exposure information and toxicity or effects information, the exposure assessment process should be coordinated with the toxicity/effects assessment. This document provides a common approach to format, which should simplify the process of reading and evaluating exposure assessments and thereby increase their utility in assessing risk.

As the Agency performs more exposure assessments, the Guidelines will be revised to reflect the benefit of experience.

II. General Guidelines and Principles

A. Exposure and Dose

Exposure has been defined by Committee E-47, Biological Effects and Environmental Fate, of the American Society for Testing and Materials, as the contact with a chemical or physical agent. The magnitude of the exposure is determined by measuring or estimating the amount of an agent available at the exchange boundaries, i.e., lungs, gut, skin, during some specified time. Exposure assessment is the determination or estimation (qualitative or quantitative) of the magnitude, frequency, duration, and route of exposure. Exposure assessments may consider past, present, and future exposures with varying techniques for each phase, i.e., modeling of future exposures, measurements of existing exposure, and biological accumulation for past exposures. Exposure assessments are generally combined with environmental and health effects data in performing risk assessments.

In considering the exposure of a subject to a hazardous agent, there are several related processes. The contact between the subject of concern and the agent may lead to the intake of some of the agent. If absorption occurs, this constitutes an uptake (or an absorbed dose) which then may lead to health effects. When biological tissue or fluid measurements indicate the presence of a chemical, exposures can be estimated from these data. Presence of a chemical in such biological samples is the most direct indication that an exposure has

occurred. The route of exposure generally impacts the overall exposure and should be considered in performing risk assessments.

B. Decision Path to Determine Scope of the Assessment

The first step in preparing an exposure assessment should be the circumscription of the problem at hand to minimize effort by use of a narrowing process. A decision logic path that describes this process is shown in Figure 1. As illustrated in Figure 1, the preliminary assessment and the in-depth assessment are two major phases in this logic path.

The preliminary assessment phase should commence by considering what risk is under study and what law might regulate the exposure to the agent. Within this framework, a preliminary data base should be compiled from readily available scientific data and exposure information based on manufacturer, processor, and user practices. Next, the most likely areas of exposure (manufacturing, processing, consumer, distribution, disposal, ambient, water and food, etc.) should be identified. Since a complete data search has not been conducted, well-identified assumptions and order of magnitude estimates are used to further narrow the exposure areas of concern.

Data from this preliminary exposure assessment can then be coupled with toxicity information to perform a preliminary risk analysis. As a result of this analysis, a decision will be made that either an in-depth exposure assessment is necessary or that there is no need for further exposure information. The organization and contents of an in-depth exposure assessment are given in the following section.

In assembling the information base for either a preliminary assessment or a more detailed assessment, its adequacy should be ascertained by addressing the following considerations:

- Availability of information in every area needed for an adequate assessment;
- Quantitative and qualitative nature of the data;
- Reliability of information;
- Limitations on the ability to assess exposure.

C. Uncertainty

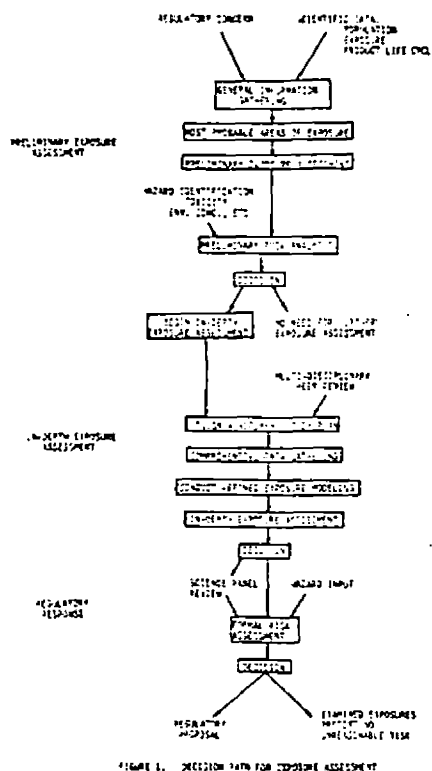
Exposure assessments are based on monitoring data, simulation model estimates, and assumptions about parameters used in approximating actual exposure conditions. Both data and assumptions contain varying degrees of uncertainty which influence the accuracy of exposure assessments. An evaluation of these uncertainties is important when the assessment is the basis for regulatory action.

The uncertainty analyses performed will vary depending on the scope of the assessment, the quantity and quality of monitoring data collected, and the type and complexity of mathematical models used. A discussion of the types of analysis used for quantifying uncertainties in exposures is presented in the next section.

III. Organization and Contents of an Exposure Assessment

A. Overview

A suggested outline for an exposure assessment document is given in Exhibit 1. The five major topics to be addressed within most exposure assessments are as follows: Source(s); Exposure Pathways; Monitored or Estimated Concentration Levels and Duration; Exposed Population(s); and Integrated Exposure Analysis. These five topics are appropriate for exposure assessments in general, whether the assessments are of global, national, regional, local, site-specific, workplace-related, or other scope. The topics are appropriate for exposure assessments on new or existing chemicals and radionuclides.



They are also applicable to both single media and multimedia assessments. Since exposure assessments are performed at different levels of detail, the extent to which any assessment contains items listed in Exhibit 1 depends upon its scope. The outline is a guide to organize the data whenever they are available.

B. Detailed Explanation of Outline

1. Executive Summary

The "Executive Summary" should be written so that it can stand on its own as a miniature report. Its main focus should be on a succinct description of the procedures used, assumptions employed, and summary tables or charts of the results. A brief discussion of the uncertainties associated with the results should be included.

2. Introduction (Purpose and Scope)

This section should state the intended purpose of the exposure assessment and identify the agent being investigated, the types of sources and exposure routes included, and the populations of concern.

Exhibit 1—Suggested Outline for an Exposure Assessment

1. EXECUTIVE SUMMARY

2. INTRODUCTION

- a. Purpose
- b. Scope

3. GENERAL INFORMATION

- a. Identity
 - (1) Molecular formula and structure, CAS number, TSL number
 - (2) Description of technical grades, contaminants, additives
 - (3) Other identifying characteristics
- b. Chemical and Physical Properties

4. SOURCES

- a. Characterization of Production and Distribution
 - (1) Production and processing
 - (2) Distribution in commerce
- b. Uses
- c. Disposal
- d. Summary of Environmental Releases

5. EXPOSURE PATHWAYS AND ENVIRONMENTAL FATE

- a. Transport and Transformation
- b. Identification of Principal Pathways of Exposure
- c. Predicting Environmental Distribution

6. MONITORED OR ESTIMATED CONCENTRATION LEVELS

- a. Summary of Monitoring Data
- b. Estimation of Environmental Concentrations
- c. Comparison of Concentration Estimates with Monitoring Data

7. EXPOSED POPULATIONS

- a. Human Populations (Size, Location, and Habits)
 - (1) Population size and characteristics
 - (2) Population location
 - (3) Population habits
- b. Nonhuman Populations (where appropriate)

- (1) Population size and characteristics
 - (2) Population location
 - (3) Population habits
- #### 8. INTEGRATED EXPOSURE ANALYSIS
- a. Calculation of Exposure
 - (1) Identification and characterization of the exposed populations and critical elements of the ecosystem
 - (2) Pathways of exposure
 - b. Human Dosimetry and Monitoring
 - c. Development of Exposure Scenarios and Profiles
 - d. Evaluation of Uncertainty
- #### 9. REFERENCES
- #### 10. APPENDICES

3. General Information

- a. Identity. (1) Molecular formula and structure, synonyms, Chemical Abstract Service number, Toxic Substance List number.

- (2) Description of technical grades, contaminants, additives.

- (3) Other identifying characteristics.

- b. Chemical and Physical Properties. This subsection should provide a summary description of the chemical and physical properties of the agent. Particular attention should be paid to the features that would affect its behavior in the environment. Examples of factors to be included are molecular weight, density, boiling point, melting point, vapor pressure, solubility, pK_a , partition coefficients, and half-lives.

4. Sources

The points at which a hazardous substance is believed to enter the environment should be described, along with any known rates of entry. Points of entry may be indoors as well as outdoors, and environments include indoor settings such as offices as well as outdoor environments. A detailed exposure assessment should include a study of sources, production, uses, destruction/disposal, and environmental release of a substance. The studies should include a description of human activities with respect to the substance and the environmental releases resulting from those activities. It should account for the controlled mass flow of the substance from creation to destruction and provide estimates of environmental releases at each step in this flow. Seasonal variations in environmental releases should also be examined. All sources of the substances should be accounted for with the sum of the uses, destruction, and the environmental releases. The environmental releases can be described in terms of geographic and temporal distribution and the receiving environmental media, with the form identified at the various release points.

- a. Characterization of Production and Distribution. All sources of the

substance's release to the environment, consistent with the scope of the assessment, should be included, such as production, extraction, processing, imports, stockpiles, transportation, accidental/incidental production as a side reaction, and natural sources. The sources should be located, and activities involving exposure to the substance should be identified.

- b. Uses. The substance should be traced from its sources through various uses (with further follow-up on the products made to determine the presence of the original material as an impurity), exports, stockpile increases, etc.

- c. Disposal. This subsection should contain an evaluation of disposal sites and destruction processes, such as incineration of industrial chemical wastes, incineration of the substance as part of an end-use item in municipal waste, landfilling of wastes, biological destruction in a secondary wastewater treatment plant, or destruction in the process of using the end product. Hazardous contaminants of the substance may be included, and products containing the substance as a contaminant may be followed from production through destruction/disposal.

- d. Summary of Environmental Releases. Estimates should be made of the quantities of the substances released to the various environmental media. Sources of release to the environment include production, use, distribution/transport, natural sources, disposal, and contamination of other products. Environmental releases should be presented at a reasonable level of detail. Extremely detailed exposure estimates would attempt to specify the following information for each significant emission source: Location, amount of the substances being released as a function of time to each environmental medium, physical characteristics of the emission source, and the physical and chemical form of the substance being released. Evaluation of the uncertainties associated with the emission estimates should be given. A detailed discussion of procedures for estimating uncertainty is presented in section 8.d.

5. Exposure Pathways and Environmental Fate

The exposure pathways section should address how a hazardous agent moves from the source to the exposed population or subject. For a less detailed assessment, broad generalizations on environmental pathways and fate may be made. In the absence of data, e.g., for new substances, fate estimates may

have to be predicted by analogy with data from other substances. Fate estimates may also be made by using models and/or monitoring data and laboratory-derived process rate coefficients. At any level of detail, certain pathways may be judged insignificant and not pursued further.

For more detailed assessments involving environmental fate, the sources analysis described previously should provide the amount and rate of emissions to the environment, and possibly the locations and form of the emissions. The environmental pathways and fate analysis follows the substance from its point of initial environmental release, through the environment, to its ultimate fate. It may result in an estimation of the geographic and temporal distribution of concentrations of the substance in the various contaminated environmental media.

a. *Transport and transformation.* The substance, once released to the environment, may be transported (e.g., convected downstream in water or on suspended sediment, through the atmosphere, etc.) or physically transformed (e.g., volatilized, melted, absorbed/desorbed, etc.); may undergo chemical transformation such as photolysis, hydrolysis, oxidation, reduction; may undergo biotransformation such as biodegradation; or may accumulate in one or more media. Thus, the environmental behavior of a substance should be evaluated before exposures are assessed. Factors that should be addressed include:

- How does the agent behave in air, water, soil, and biological media? Does it bioaccumulate or biodegrade? Is it absorbed or taken up by plants?
- What are the principal mechanisms for change or removal in each of the environmental media?
- Does the agent react with other compounds in the environment?
- Is there intermedia transfer? What are the mechanisms for intermedia transfer? What are the rates of the intermedia transfer or reaction mechanisms?
- How long might the agent remain in each environmental medium? How does its concentration change with time in each medium?
- What are the products into which the agent might degrade or change in the environment? Are any of these degradation products ecologically or biologically harmful? What is the environmental behavior of the harmful products?
- Is a steady-state concentration distribution in the environment, or in

specific segments of the environment, achieved? If not, can the nonsteady-state distribution be described?

- What is the resultant distribution in the environment—for different media, different types or forms of the agent, for different geographical areas, at different times or seasons?

b. *Identification of Principal Pathways of Exposure.* The principal pathway analysis should evaluate the sources, locations, and types of environmental releases, together with environmental behavioral factors, to determine the significant routes of human and environmental exposure to the substance. Thus, by listing the important characteristics of the environmental release (entering media, emission rates, etc.) and the agent's behavior (intermedia transfer, persistence, etc.) after release to each of the entering media, it should be possible to follow the movement of the agent from its initial release to its subsequent fate in the environment. At any point in the environment, human or environmental exposure may occur. Pathways that result in major concentrations of the agent and high potential for human or environmental contact are the principal exposure pathways.

c. *Predicting Environmental Distribution.* Models may be used to predict environmental distributions of chemicals. Many modeling estimates of environmental distribution of chemicals are based in part on monitoring data. In predicting environmental distributions of chemicals, available monitoring data should be considered.

In this section an estimation is made, using appropriate models, of representative concentrations of the agent in different environmental media, and its time-dependence in specific geographical locations (e.g., river basins, streams, etc.).

6. Monitored or Estimated Concentration Levels

a. *Summary of Monitoring Data.* Monitoring data are used to identify releases (source terms) and, in the exposure pathways and fate assessments, to quantitatively estimate both release rates and environmental concentrations. Some examples of uses of monitoring data are: Sampling of stacks of discharge pipes for emissions to the environment; testing of products for chemical or radionuclide content; testing of products for chemical or radioactive releases; sampling of appropriate points within a manufacturing plant to determine releases from industrial processes or practices; and sampling of solid waste

for chemical or radionuclide content. These data should be characterized as to accuracy, precision, and representativeness. If actual environmental monitoring data are unavailable, concentrations can be estimated by various means, including the use of fate models (see previous section) or, in the case of new chemicals, by analogy with existing chemicals.

The analysis of monitoring data should be considered a complement to environmental pathway and fate analysis for the following reasons: For most pollutants, particularly organic and new chemicals, monitoring data are limited; analysis of monitoring data does not often yield relationships between environmental releases and environmental concentration distribution in media or geographic locations that have not been monitored; analysis of monitoring data does not provide information on how and where biota influence the environmental distribution of a pollutant; and monitored concentrations may not be traceable to individual sources that EPA can regulate. Monitoring data are, however, a direct source of information for exposure analysis and, furthermore, they can be used to calibrate or extrapolate models or calculations to assess environmental distribution.

b. *Estimation of Environmental Concentrations.* Concentrations of agents should be estimated for all environmental media that might contribute to significant exposures. Generally, the environmental concentrations are estimated from monitoring data, mathematical models, or a combination of the two.

The concentrations must be estimated and presented in a format consistent with available dose-response information. In some cases an estimate of annual average concentration will be sufficient, while in other cases the temporal distribution of concentrations may be required. Future environmental concentrations resulting from current or past releases may also be projected. In some cases, both the temporal and geographic distributions of the concentration may be assessed. Moreover, if the agent has natural sources, the contribution of these to environmental concentrations may be relevant. These "background" concentrations may be particularly important when the results of tests of toxic effects show a threshold or distinctly nonlinear dose-response.

The uncertainties associated with the estimated concentrations should be evaluated by an analysis of the

uncertainties of the model parameters and input variables. When the estimates of the environmental concentrations are based on mathematical models, the model results should be compared to available monitoring data, and any significant discrepancies should be discussed. Reliable, analytically-determined values should be given precedence over estimated values whenever significant discrepancies are found.

7. Exposed Populations

Populations selected for study may be done *a priori*, but frequently the populations will be identified as a result of the sources and fate studies. From an analysis of the distribution of the agent, populations convected and subpopulations (i.e., collections of subjects) at potentially high exposure can be identified, which will then form the basis for the populations studied. Subpopulations of high sensitivity, such as pregnant women, infants, chronically ill, etc., may be studied separately.

In many cases, exposed populations can be described only generally. In some cases, however, more specific information may be available on matters such as the following:

a. *Human Populations.* (1) *Population size and characteristics (e.g., trends, sex/age distribution)*

(2) *Population location*

(3) *Population habits—transportation habits, eating habits, recreational habits, workplace habits, product use habits, etc.*

b. *Nonhuman Populations (where appropriate).* (1) *Population size and characteristics (e.g., species, trends)*

(2) *Population location*

(3) *Population habits*

Census and other survey data may be used to identify and describe the population exposed to various contaminated environmental media. Depending on the characteristics of available toxicological data, it may be appropriate to describe the exposed population by other characteristics such as species, race-age-sex distribution, and health status.

8. Integrated Exposure Analysis

The integrated exposure analysis combines the estimation of environmental concentrations (sources and fate information) with the description of the exposed population to yield exposure profiles. Data should be provided on the size of the exposed populations; duration, frequency, and intensity of exposure; and routes of exposure. Exposures should be related to sources.

For more detailed assessments, the estimated environmental concentrations should be considered in conjunction with the geographic distribution of the human and environmental populations. The behavioral and biological characteristics of the exposed populations should be considered and the exposures of populations to various concentration profiles should be estimated. The results can be presented in tabular or graphic form, and an estimate of the uncertainty associated with them should be provided.

a. *Calculations of Exposure.* The calculation of exposure involves two major aspects:

(1) *Identification of the Exposed Population and Critical Elements of the Ecosystem.*

The estimate of environmental concentrations also should give the geographical areas and environmental media contaminated. The stated purpose of the assessment should have prescribed the human and environmental subjects for which exposures are to be calculated. If the subjects are not listed, the contaminated geographical areas and environmental media can be evaluated to determine subject populations. The degree of detail to be used in defining the exposed population distribution depends on the concentration gradient over geographic areas.

(2) *Identification of pathways of exposure.*

(a) *Identification and description of the routes by which the substances travel from production site, through uses, through environmental releases/sources, through transport and fate processes, to the target population.*

(b) *Quantitative estimates of the amounts of the chemical following each exposure pathway. Such estimates allow the various pathways to be put in the perspective of relative importance.*

From the geographic and temporal distribution of environmental concentrations, the exposed population, the behavioral characteristics, and the critical elements of the ecosystem, exposure distributions can be estimated. The results of exposure calculation should be presented in a format that is consistent with the requirements of the dose-response functions which may later be used in a risk assessment. For example, when health risks caused by exposure over extended durations are considered, average daily exposure over the duration of exposure usually is calculated. When lifetime risks are considered, average daily exposure over a lifetime usually is calculated. In contrast, when health risks caused by exposures over short durations are

considered, exposure rates are calculated over short time intervals to ensure that peak risks are defined. Many exposure assessments are based on the average exposure occurring over the exposure period. The range of possible exposures is usually divided into intervals, and the exposures within each interval are counted. The results can be presented in a tabular form or as a histogram.

The population residing in a specific geographic area may be exposed to a substance from several exposure routes. For each exposure route, exposure of individuals in these populations may be determined by summing the contribution of all sources to the exposure route. When exposures involve more than one exposure route, the relative amounts of a substance absorbed is usually route dependent. Consequently, total absorbed dose estimates must account for these differences. Because EPA regulates sources of releases, the contribution to exposures from each type of source being considered should be displayed. Exposure estimates should be presented for each significant exposure route (i.e., those routes consistent with the regulatory purpose), and the results should be tabulated in such a way that total externally applied and absorbed dose can be determined.

b. *Human Dosimetry and Monitoring.* Biological monitoring of human body fluids and tissues for substances or their metabolites can be used to estimate current or past exposure to chemicals. When analytical methods are available, chemicals that have been absorbed into the body can be measured in body tissue and fluid. Such measurements can be used to estimate exposures. However, the substances to which humans are exposed are highly variable in the degree to which they leave in the body reliable indicators of exposure. Furthermore, although a compound may be relatively easy to detect in body tissue, for some compounds, attributing body burdens to specific environmental releases may be difficult because of limited ability to obtain environmental monitoring data.

c. *Development of Exposure Scenarios and Profiles.* Depending on the scope of the exposure assessment, the total exposure may be fractionated into one or more "exposure scenarios" to facilitate quantification. As an example, Table 1 lists seven very broad scenarios: Occupational, Consumer, Transportation, Disposal, Food, Drinking Water, and Ambient. For each of the scenarios, the major topics necessary to quantify exposure include sources, pathways, monitoring, and population

characteristics. Investigation of only one scenario may be necessary for the scope of some assessments. For example, a pesticide application exposure assessment may consider the

occupational scenario which would address the exposure to applicators and populations in the vicinity of the site. An exposure assessment around a hazardous waste site may focus on the

disposal scenario. The exposure assessment also may consider other scenarios. The more extensive and comprehensive the scope, the more scenarios are usually involved.

TABLE 1. EXPOSURE ASSESSMENT NEEDS FOR VARIOUS EXPOSURE SCENARIOS

Exposure scenario	Source needs	Fate needs	Population characteristics needs	Monitoring needs
Occupational (chemical production)	Site/plant locations in-plant/on-site materials balance.	Physical and chemical properties models.	Workers, families, population around site/plants.	In-plant/on-site releases, ambient levels surrounding site/plant human monitoring. Levels in products released.
Consumer (direct use of chemical or inadvertent use).	Consumption rates, distribution patterns in products.	Physical and chemical properties, shelf life release rates, models.	Consumers.	
Transportation/storage/spills	Patterns of distribution and transportation; models for spills.	Physical and chemical properties, environmental fate models.	Storage, transportation workers, general population in area.	Releases, ambient levels.
Disposal (include incineration, landfill).	Materials balance around disposal method, efficiency, releases to environment.	Fate within disposal process; environmental fate of releases; models.	Workers at site of disposal, general population around site.	Releases, levels at various point within process, ambient levels.
Food	Food chain, packaging, additives.	Food chain models, fate during preparation or processing of food.	General population, nonhuman population.	Levels in food, feedstuff; food chain sampling.
Drinking water	Groundwater, surface water, distribution system.	Leach rates from pipes, chlorination processes, fate in water; models.	General population.	Levels in drinking water, groundwater, surface water, treatment plants.
Ambient	Releases to environment; air, land, water.	Environmental fate models.	General population, nonhuman population.	Ambient air, water, soil, etc.; human monitoring.

It will usually be advantageous in performing an exposure assessment to identify exposure scenarios, quantify the exposure in each scenario, and then integrate the scenarios to estimate total exposure. In this "integrated exposure analysis," summation of independent exposures from different scenarios (keeping exposure routes separate) often will result in a breakout of exposure by subpopulations, since the individual scenarios usually treat exposure by subpopulation. Therefore, the integration of the scenarios, or integrated exposure analysis, will often result in an exposure profile.

For each exposed subpopulation, exposure profiles should include the size of the group, the make-up of the group (age, sex, etc.), the source of the agent, the exposure pathways, the frequency and the intensity of exposure by each route (dermal, inhalation, etc.), duration of exposure, and the form of the agent when exposure occurs. Assumptions and uncertainties associated with each scenario and profile should be clearly discussed.

d. Evaluation of Uncertainty. (1) *Introduction.* Often an exposure assessment progresses through several stages of refinement. The purpose of these Guidelines is to present methods appropriate for characterization of uncertainty for assessments at various stages of refinement, from assessments based upon limited initial data to those based upon extensive data.

The appropriate method for characterizing uncertainty for an exposure assessment depends upon the underlying parameters being estimated, the type and extent of data available, and the estimation procedures utilized.

The uncertainty of interest is always with regard to the population characteristic being estimated. For example, when the population distribution of exposures is being estimated, characterization of uncertainty addresses the possible differences between the estimated distribution of exposure and the true population distribution of exposure.

An exposure assessment quantifies contact of a substance with affected population members (human or nonhuman subjects). The measure of contact (e.g., environmental level of absorbed dose) depends upon what is needed to predict risk. An integrated exposure assessment quantifies this contact via all routes of exposure (inhalation, ingestion, and dermal) and all exposure pathways (e.g., occupational exposure, exposure from consumption of manufactured goods, etc.). The exposed population generally is partitioned into subpopulations such that the likely exposure of all members of a subpopulation is attributable to the same sources. The exposure for each member of a subpopulation is then the sum of exposures over a fixed set of sources and pathways. The measured or estimated exposures for members of a subpopulation are ideally used to estimate the subpopulation distribution of exposure or characteristics thereof. However, a lack of sufficient information sometimes precludes estimation of the subpopulation distributions of exposure and only summary measures of this distribution, such as the mean, minimum, maximum, etc., are estimated. In each case characterization of uncertainty for the exposure assessment primarily

addresses limitations of the data and the estimation procedures. The proportions of the population members in the individual subpopulations are usually estimated and can be used (by combining estimated distributions for the subpopulations) to estimate the distribution of exposure for the total population. Uncertainty concerning the sizes of the subpopulations should be addressed by discussing limitations of the data and estimation methods as well as by tabulating confidence interval estimates for the population sizes, whenever possible.

(2) *Assessments Based Upon Limited Initial Data.* The initial exposure assessment for a substance may be based upon limited data for exposure and/or input variables for an exposure prediction model (i.e., an equation that expresses exposure as a function of one or more input variables). These data might be either extant data or data produced by an initial small-scale study. The initial limited data frequently are insufficient to permit estimation of the entire distribution of exposure. Instead, summary measures of this distribution, such as the mean, minimum, and maximum, are usually estimated.

If the assessment is based upon measured exposures, the methods used to characterize uncertainty depend mainly upon whether or not the data result from a probability sample for which the probability of inclusion is known for each sample member. Characterization of uncertainty for an assessment based upon a probability sample of exposures is discussed later in section 8. d. (5). If the measured exposures are not based upon a probability sample, acknowledgement

that no strictly valid statistical inferences can be made beyond the units actually in the sample is one aspect of the characterization of uncertainty. If inference procedures are implemented, the assumptions upon which these inferences are based (e.g., treatment of the sample as if it was a simple random sample, or assumption of an underlying model) should be explicitly stated and justified. The data collection methods and inherent limitations of the data should also be discussed.

An initial exposure assessment also may be based upon limited data, such as estimated ranges, for input variables for an exposure prediction model. The exposure prediction model would be derived from a postulated exposure scenario that describes the pathways from sources to contact with population members. If the data were only sufficient to support estimates of the ranges of the input variables, the exposure assessment might be limited to a sensitivity analysis. The purpose of the sensitivity analysis would be to identify influential model input variables and develop bounds on the distribution of exposure. A sensitivity analysis would estimate the range of exposures that would result as individual model input variables were varied from their minimum to their maximum possible values with the other input variables held at fixed values, e.g., their midranges. The overall minimum and maximum possible exposures usually would be estimated also. For an exposure assessment of this type, the uncertainty would be characterized by describing the limitations of the data used to estimate plausible ranges of model input variables and by discussing justification for the model. Justification of the model should include a description of the exposure scenario, choice of model input variables, and the functional form of the model. Sensitivity to the model formulation also can be investigated by replicating the sensitivity analysis for plausible alternative models.

If the maximum possible exposure estimated by the sensitivity analysis presented no significant health risk, there might be no need to refine the assessment. If both the minimum and maximum exposures presented a potentially significant health risk, it would be known that the exposure scenario represented a significant health problem without refining the assessment. When the minimum exposure estimate does not present a potentially significant health risk and maximum dose, then greater importance

is placed on choosing a summary parameter of the exposure distribution (e.g., the mean or percentile) as the basis for a regulatory decision. Refining the exposure assessment to estimate the distribution of exposure permits selection of any summary parameter (minimum, maximum, mean, or percentile, etc.) as the basis for regulatory decision.

The sensitivity analysis can be enhanced by computing the predicted exposures that result from all possible input variable combinations. If each input variable has only a finite set of possible values, the set of all possible combinations of the input variables can be formed, and the predicted exposure can be computed for each combination. These exposure predictions can be used to form a distribution of exposures by counting the number of occurrences of each exposure level or interval of exposures. This is equivalent to estimating the distribution of exposures that results from treating all input variable combinations as equally likely. This procedure can also be applied by discretizing continuous input variables and representing them by equally-spaced points. In the limit, as the equal spaces become small and the number of points becomes large, the distribution of exposure that results from counting occurrences of exposure levels is equivalent to estimating the distribution of exposures that results from statistically-independent, continuous input variables with uniform distributions on the estimated ranges. This estimated distribution of exposure values can be produced by the methods of mathematical statistics or Monte Carlo simulation. The Monte Carlo method consists of randomly generating input variable values and using these to compute corresponding exposure levels, generating an exposure distribution via many iterations. Interpretation of statistics based upon this exposure distribution would be in terms of the equally likely input variable combinations. For example, the 95th percentile of this distribution would be the exposure level exceeded by only 5% of the exposures resulting from treating all combinations of input variable values as equally likely. Although this distribution of exposures cannot be interpreted as an estimate of the population distribution (unless the input variables actually are statistically independent and uniformly distributed), it provides additional information for making regulatory decisions. Characterization of uncertainty would include a discussion of limitations of the data and justification for the model as

discussed above. Sensitivity to model formulation could also be investigated by estimating the distribution of exposure that results from using the same uniform input variable distributions with plausible alternative models and comparing the estimated percentiles.

(3) *Assessments Based Upon Subjective Estimates of Input Variable Distributions.* If a model has been formulated that expresses exposure as a function of one or more input variables, the methods of mathematical statistics or Monte Carlo simulation can be used to estimate the population distribution of exposure from an estimate of the joint distribution of the model input variables. Ideally model input variables should be represented by empirically validated probability distributions. In some cases, it may be possible to formulate an estimate of the joint distribution of model input variables from discussions with subject-matter experts (e.g., via histograms for statistically-independent input variables). The estimated population distribution of exposure will be equivalent to the distribution discussed in section 8. d. (2) for equally likely combinations of input variable values only when the input variable distributions supported are independent uniform distributions. When qualitative knowledge of input variable distributions is used to estimate the population distribution of exposure, uncertainty is characterized by discussing justification for the presumed model and input variable distributions. Alternative models and/or alternative input variable distributions also should be discussed. Sensitivity to these alternatives can be investigated by estimating the distributions of exposure that result from plausible alternatives and comparing the percentiles of the estimated exposure distributions. All available data, even if data are limited, should be used to validate the presumed input variable distributions and the predicted distribution of exposure.

(4) *Assessments Based Upon Data for Model Input Variables.* The exposure assessment based upon an estimate of the joint probability distribution for model input variables can be refined by collecting sample survey data for model input variables for a sample of population members. The population distribution of exposure can then be estimated by computing the expected exposure for each sample member based upon the model. These expected exposures can be used to directly compute confidence interval estimates for percentiles of the exposure

distribution. Alternatively, the sample survey data can be used to compute joint confidence interval estimates for percentiles of the input variable distribution, which can then be used to generate confidence interval estimates for percentiles of the exposure distribution. In either case, the interval estimates for percentiles of the exposure distribution are a useful quantitative characterization of uncertainty.

Characterization of uncertainty for the exposure assessment would contain a thorough discussion of limitations of the data and justification for the model used to compute expected exposures. The design of the sample survey used to produce the data base should also be discussed. If a probability sample were not used, the lack of a probability sample would be an additional source of uncertainty. Any assumptions used in computing the confidence interval estimates, such as independence of model input variables, should be explicitly stated and justified. Sensitivity to model formulation can be investigated by estimating the distribution of exposure for plausible alternative models and comparing the estimated percentiles, if sample survey data have been collected for the input

variables of the alternative models. Appropriate available data for exposure should be used to validate the predicted distribution of exposure. If specific probability distributions have been presumed for any model input variables, the data for these variables should be used to test for goodness of fit for these distributions.

(5) *Assessments Based Upon Data for Exposure.* A major reduction in the uncertainty associated with an exposure assessment can be achieved by directly measuring the exposure for a sufficiently large sample of members of the affected population. This reduction in uncertainty is achieved by eliminating the use of a model to predict exposure. The measured exposure levels can be used to directly estimate the population distribution of exposure and confidence interval estimates for percentiles of the exposure distribution. Direct confidence interval estimates also can be computed for other characteristics of the exposure distribution, such as the mean exposure.

These confidence interval estimates are then the primary characterization of uncertainty for the exposure assessment. Limitations of the data and design of the sample survey used to collect the data also should be

discussed. If the sample was not a probability sample, this would again be an additional source of uncertainty.

(6) *Summary.* A summary of the primary methods recommended for characterizing uncertainty in exposure assessments is presented in Table 2. Virtually all exposure assessments, except those based upon measured exposure levels for a probability sample of population members, rely upon a model to predict exposure. The model may be any mathematical function, simple or complex, that expresses an individual's exposure as a function of one or more input variables. Whenever a model that has not been validated is used as the basis for an exposure assessment, the uncertainty associated with the exposure assessment may be substantial. The primary characterization of uncertainty is at least partly qualitative in this case, i.e., it includes a description of the assumptions inherent in the model and their justification. Plausible alternative models should be discussed. Sensitivity of the exposure assessment to model formulation can be investigated by replicating the assessment for plausible alternative models.

TABLE 2.—SUMMARY OF PRIMARY METHODS FOR CHARACTERIZING UNCERTAINTY FOR EXPOSURE ASSESSMENTS

Type and extent of data	Population characteristic being estimated	Primary methods for characterizing uncertainty	
		Qualitative methods	Quantitative methods
Measured exposures for a large sample of population members.	Distribution of exposure.....	1. Limitations of the survey design and measurement techniques.	1. Confidence interval estimates for percentiles of the exposure distribution. 2. Goodness of fit for exposure models, if any have been postulated.
Measured exposures for a small sample of population members.	Summary parameter(s) of the exposure distribution, e.g., mean or a percentile.	1. Limitations of the survey design and measurement techniques.	1. Confidence interval estimates for the summary parameter(s). 2. Goodness of fit for exposure models, if any have been postulated.
Measured model input variables for a large sample of population members.	Distribution of exposure.....	1. Limitations of the survey design and measurement techniques. 2. Validity of the exposure model	1. Confidence interval estimates for percentiles of the exposure distribution. 2. Goodness of fit for input variable distribution functions, if any have been postulated. 3. Estimated distribution of exposure based upon alternative models.
Estimated distributions of model input variables.	Distribution of exposure.....	1. Validity of the exposure model 2. Limitations of the data or other basis for the input variable distributions.	1. Confidence interval estimates for percentiles of the exposure distribution. 2. Goodness of fit for input variable distributions, if input variable data are available. 3. Estimated distribution of exposure based upon alternative models.
Limited data for model input variables.....	Minimum, maximum, and range of the exposure distribution.	1. Limitations of the data. 2. Validity of the exposure model	1. If input variable data are very limited, e.g., some infant data collected for other purposes, quantitative characterization of uncertainty may not be possible.

When an exposure assessment is based upon directly measured exposure levels for a probability sample of population members, uncertainty can be greatly reduced and described quantitatively. In this case, the primary sources of uncertainty are measurement errors and sampling errors. The effects of these sources of error are measured quantitatively by confidence interval estimates of percentiles of the exposure

distribution. Moreover, the sampling errors can be limited by taking a large sample.

Whenever the latter is not feasible, it is sometimes possible to obtain at least some data for exposure and model input variables. These data should be used to assess goodness of fit of the model and/or presumed distributions of input variables. This substantially reduces the amount of quantitative uncertainty for

estimation of the distribution of exposure and is strongly recommended. It is recognized, however, that it may not be feasible to collect such data.

9. References

The references should contain a listing of all reports, documents, articles, memoranda, contacts, etc. that have been cited in the report.

10. Appendices

The appendices may contain such items as memoranda and letters that are not readily accessible, other tables of monitoring data, detailed lists of emission sources, detailed tables of exposures, process flow diagrams, mathematical model formulations, or any other item that may be needed to describe or document the exposure assessment.

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