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1. INTRODUCTION

1.1. BACKGROUND AND PURPOSE

Some of the steps for performing an exposure assessment are (1) identifying the source of the environmental contamination and the media that transports the contaminant; (2) determining the contaminant concentration; (3) determining the exposure scenarios, and pathways and routes of exposure; (4) determining the exposure factors related to human behaviors that define time, frequency, and duration of exposure; and (5) identifying the exposed population. Exposure factors are factors related to human behavior and characteristics that help determine an individual's exposure to an agent. The National Academy of Sciences (NAS) report on *Risk Assessment in the Federal Government: Managing the Process* and subsequent publication of the U.S. Environmental Protection Agency's (EPA) exposure guidelines in 1986 identified the need for summarizing exposure factors data necessary for characterizing some of the steps outlined above (U.S. EPA, 1987a; NRC, 1983). Around the same time, the U.S. EPA published a report entitled *Development of Statistical Distributions or Ranges of Standard Factors Used in Exposure Assessment* to support the 1986 exposure guidelines and to promote consistency in U.S. EPA's exposure assessment activities (U.S. EPA, 1985). The exposure assessment field continued to evolve and so did the need for more comprehensive data on exposure factors. The *Exposure Factors Handbook* was first published in 1989 and updated in 1997 in response to this need (U.S. EPA, 1997a, 1989a). This current edition is the update of the 1997 handbook (U.S. EPA, 1997a), and it incorporates data from the *Child-Specific Exposure Factors Handbook* (U.S. EPA, 2008a) that was published in September 2008. The information presented in this handbook supersedes the *Child-Specific Exposure Factors Handbook* published in 2008 (U.S. EPA, 2008a).

The purpose of the *Exposure Factors Handbook* is to (1) summarize data on human behavioral and physiological characteristics that affect exposure to environmental contaminants, and (2) provide exposure/risk assessors with recommended values for

> Exposure factors are factors related to human behavior and characteristics that help determine an individual's exposure to an agent.

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> (1) summarize data on human behavioral and physiological characteristics
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these factors that can be used to assess exposure among both adults and children.

1.2. INTENDED AUDIENCE

The *Exposure Factors Handbook* is intended for use by exposure and risk assessors both within and outside the U.S. EPA as a reference tool and primary source of exposure factor information. It may be used by scientists, economists, and other interested parties as a source of data and/or U.S. EPA recommendations on numeric estimates for behavioral and physiological characteristics needed to estimate exposure to environmental agents.

1.3. SCOPE

This handbook incorporates the changes in risk assessment practices that were first presented in the U.S. EPA's Cancer Guidelines, regarding the need to consider life stages rather than subpopulations (U.S. EPA, 2005c, e). A life stage "refers to a distinguishable time frame in an individual's life characterized by unique and relatively stable behavioral and/or physiological characteristics that are associated with development and growth" (U.S. EPA, 2005b). The handbook emphasizes a major recommendation in U.S. EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005e) to sum exposures and risks across life stages rather than relying on the use of a lifetime average adult exposure to calculate risk. This handbook also uses updated information to incorporate any new exposure factors data/research that have become available since it was last revised in 1997 and is consistent with the U.S. EPA's new set of standardized childhood age groups (U.S. EPA, 2005b), which are recommended for use in exposure assessments. Available data through July 2011 are included in the handbook.

The recommendations presented in this handbook are not legally binding on any U.S. EPA program and should be interpreted as suggestions that program offices or individual exposure assessors can consider and modify as needed. The recommendations provided in this handbook do not supersede standards or guidance established by U.S. EPA program offices, states, or other risk assessment organizations outside the Agency (e.g.,

World Health Organization, National Research Council). Many of these factors are best quantified on a site- or situation-specific basis. The decision as to whether to use site-specific or national values for an assessment may depend on the quality of the competing data sets as well as on the purpose of the specific assessment. The handbook has strived to include full discussions of the issues that assessors should consider in deciding how to use these data and recommendations.

This document does not include chemical-specific data or information on physiological parameters that may be needed for exposure assessments involving physiologically based pharmacokinetic (PBPK) modeling. Information on the application of PBPK models and supporting data are found in U.S. EPA (2006a) and Lipscomb (2006).

1.4. UPDATES TO PREVIOUS VERSIONS OF THE HANDBOOK

All chapters have been revised to include published literature up to July 2011. Some of the main revisions are highlighted below:

- Added food and water intake data obtained from the National Health and Nutrition Examination Survey (NHANES) 2003–2006;
- Added fat intake data and total food intake data;
- Added new chapter on non-dietary factors;
- Updated soil ingestion rates for children and adults;
- Updated data on dermal exposure and added information on other factors such as film thickness of liquids to skin, transfer of residue, and skin thickness;
- Updated fish intake rates for the general population using data obtained from NHANES 2003–2006;
- Updated body-weight data with National Health and Nutrition Examination Survey 1999–2006;
- Added body-weight data for pregnant/lactating women and fetal weight;
- Updated children's factors with new recommended age groupings (U.S. EPA, 2005b);
- Updated life expectancy data with U.S. Census Bureau data 2006;
- Updated data on human milk ingestion and prevalence of breast-feeding; and

- Expanded residential characteristics chapter to include data from commercial buildings.

1.5. SELECTION OF STUDIES FOR THE HANDBOOK AND DATA PRESENTATION

Many scientific studies were reviewed for possible inclusion in this handbook. Although systematic literature searches were initially conducted for every chapter, much of the literature was identified through supplementary targeted searches and from personal communications with researchers in the various fields. Information in this handbook has been summarized from studies documented in the scientific literature and other publicly available sources. As such, this handbook is a compilation of data from a variety of different sources. Most of the data presented in this handbook are derived from studies that target (1) the general population (e.g., Center for Disease Control and Prevention [CDC] NHANES) or (2) a sample population from a specific area or group (e.g., fish consumption among Native American children). With very few exceptions, the data presented are the analyses of the individual study authors. Since the studies included in this handbook varied in terms of their objectives, design, scope, presentation of results, etc., the level of detail, statistics, and terminology may vary from study to study and from factor to factor. For example, some authors used geometric means to present their results, while others used arithmetic means or distributions. Authors have sometimes used different terms to describe the same racial/ethnic populations. Within the constraint of presenting the original material as accurately as possible, the U.S. EPA has made an effort to present discussions and results in a consistent manner and using consistent terminology. The strengths and limitations of each study are discussed to provide the reader with a better understanding of the uncertainties associated with the values derived from the study.

If it is necessary to characterize a population that is not directly covered by the data in this handbook, the risk or exposure assessor may need to evaluate whether these data may be used as suitable substitutes for the population of interest or whether there is a need to seek additional population-specific data. If information is needed for identifying and enumerating populations who may be at risk for greater contaminant exposures or who exhibit a heightened sensitivity to particular chemicals, refer to *Socio-demographic Data Used for Identifying Potentially Highly Exposed Populations* (U.S. EPA, 1999).

Studies were chosen that were seen as useful and appropriate for estimating exposure factors for both adults and children. In conjunction with the *Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants* (U.S. EPA, 2005b), this handbook adopted the age group notation "X to <Y" (e.g., the age group 3 to <6 years is meant to span a 3-year time interval from a child's 3rd birthday up until the day before his or her 6th birthday). Every attempt was made to present the data for the recommended age groups. In cases where age group categories from the study authors did not match exactly with the U.S. EPA recommended age groups, the recommendations were matched as closely as possible. In some cases, data were limited, and age groups were lumped into bigger age categories to obtain adequate sample size. It is also recognized that dose-response data may not be available for many of the recommended age groupings. However, a standard set of age groups can assist in data collection efforts and provide focus for future research to better assess all significant variations in life stage (U.S. EPA, 2005b). To this date, no specific guidance is available with regard to age groupings for presenting adult data. Therefore, adult data (i.e., >21 years old) are presented using the age groups defined by the authors of the individual studies. No attempt was made to reanalyze the data using a consistent set of age groups. Therefore, in cases where data were analyzed by the U.S. EPA, age categories were defined as finely as possible based on adequacy of sample size. It is recognized that adults' activity patterns will vary with many factors including age, especially in the older adult population.

Certain studies described in this handbook are designated as "key," that is, the most up-to-date and scientifically sound for deriving recommendations for exposure factors. The recommended values for all exposure factors are based on the results of the key studies (see Section 1.6). Other studies are designated "relevant," meaning applicable or pertinent, but not necessarily the most important. As new data or analyses are published, "key" studies may be moved to the "relevant" category in future revisions because they are replaced by more up-to-date data or an analysis of improved quality. Studies may be classified as "relevant" for one or more of the following reasons: (1) they provide supporting data (e.g., older studies on food intake that may be useful for trend analysis); (2) they provide information related to the factor of interest (e.g., data on prevalence of breast-feeding); (3) the study design or approach makes the data less applicable to the population of interest (e.g., studies with small sample size, studies not conducted in the United States).

It is important to note that studies were evaluated based on their ability to represent the population for which the study was designed. The users of the handbook will need to evaluate the studies' applicability to their population of interest.

1.5.1. General Assessment Factors

The Agency recognizes the need to evaluate the quality and relevance of scientific and technical information used in support of Agency actions (U.S. EPA, 2006c, 2003d, 2002). When evaluating scientific and technical information, the U.S. EPA's Science Policy Council recommends using five General Assessment Factors (GAFs): (1) soundness, (2) applicability and utility, (3) clarity and completeness, (4) uncertainty and variability, and (5) evaluation and review (U.S. EPA, 2003d). These GAFs were adapted and expanded to include specific considerations deemed to be important during evaluation of exposure factors data and were used to judge the quality of the underlying data used to derive recommendations.

1.5.2. Selection Criteria

The confidence ratings for the various exposure factor recommendations, and selection of the key studies that form the basis for these recommendations, were based on specific criteria within each of the five GAFs, as follows:

1) *Soundness: Scientific and technical procedures, measures, methods, or models employed to generate the information are reasonable for, and consistent with, the intended application.* The soundness of the experimental procedures or approaches in the study designs of the available studies was evaluated according to the following:

   a) **Adequacy of the Study Approach Used:** In general, more confidence was placed on experimental procedures or approaches that more likely or closely captured the desired measurement. Direct exposure data collection techniques, such as direct observation, personal monitoring devices, or other known methods were preferred where available. If studies utilizing direct measurement were not available, studies were selected that relied on validated indirect measurement methods such as surrogate measures (such as heart rate for

inhalation rate), and use of questionnaires. If questionnaires or surveys were used, proper design and procedures include an adequate sample size for the population under consideration, a response rate large enough to avoid biases, and avoidance of bias in the design of the instrument and interpretation of the results. More confidence was placed in exposure factors that relied on studies that gave appropriate consideration to these study design issues. Studies were also deemed preferable if based on primary data, but studies based on secondary sources were also included where they offered an original analysis. In general, higher confidence was placed on exposure factors based on primary data.

b) **Minimal (or Defined) Bias in Study Design:** Studies were sought that were designed with minimal bias, or at least if biases were suspected to be present, the direction of the bias (i.e., an overestimate or underestimate of the parameter) was either stated or apparent from the study design. More confidence was placed on exposure factors based on studies that minimized bias.

2) *Applicability and Utility: The information is relevant for the Agency's intended use. The applicability and utility of the available studies were evaluated based on the following criteria:*

a) **Focus on Exposure Factor of Interest:** Studies were preferred that directly addressed the exposure factor of interest or addressed related factors that have significance for the factor under consideration. As an example of the latter case, a selected study contained useful ancillary information concerning fat content in fish, although it did not directly address fish consumption.

b) **Representativeness of the Population:** More confidence was placed in studies that addressed the U.S. population. Data from populations outside the United States were sometimes included if behavioral patterns or other characteristics of exposure were similar. Studies seeking to characterize a particular region or demographic characteristic were selected, if appropriately representative of that population. In cases where data were limited, studies with limitations in this area were included, and limitations were

noted in the handbook. Higher confidence ratings were given to exposure factors where the available data were representative of the population of interest. The risk or exposure assessor may need to evaluate whether these data may be used as suitable substitutes for their population of interest or whether there is a need to seek additional population-specific data.

c) **Currency of Information:** More confidence was placed in studies that were sufficiently recent to represent current exposure conditions. This is an important consideration for those factors that change with time. Older data were evaluated and considered in instances where the variability of the exposure factor over time was determined to be insignificant or unimportant. In some cases, recent data were very limited. Therefore, the data provided in these instances were the only available data. Limitations on the age of the data were noted. Recent studies are more likely to use state-of-the-art methodologies that reflect advances in the exposure assessment field. Consequently, exposure factor recommendations based on current data were given higher confidence ratings than those based on older data, except in cases where the age of the data would not affect the recommended values.

d) **Adequacy of Data Collection Period:** Because most users of the handbook are primarily addressing chronic exposures, studies were sought that utilized the most appropriate techniques for collecting data to characterize long-term behavior. Higher confidence ratings were given to exposure factor recommendations that were based on an adequate data collection period.

3) *Clarity and Completeness: The degree of clarity and completeness with which the data, assumptions, methods, quality assurance, sponsoring organizations and analyses employed to generate the information is documented.* Clarity and completeness were evaluated based on the following criteria:

a) **Accessibility:** Studies that the user could access in their entirety, if needed, were preferred.

b) **Reproducibility:** Studies that contained sufficient information so that methods could be reproduced, or could be

evaluated, based on the details of the author's work, were preferred.

c) **Quality Assurance:** Studies with documented quality assurance/quality control measures were preferred. Higher confidence ratings were given to exposure factors that were based on studies where appropriate quality assurance/quality control measures were used.

4) *Variability and Uncertainty: The variability and uncertainty (quantitative and qualitative) in the information or the procedures, measures, methods, or models are evaluated and characterized.* Variability arises from true heterogeneity across people, places, or time and can affect the precision of exposure estimates and the degree to which they can be generalized. The types of variability include spatial, temporal, and inter-individual. Uncertainty represents a lack of knowledge about factors affecting exposure or risk and can lead to inaccurate or biased estimates of exposure. Increasingly probabilistic methods are being utilized to analyze variability and uncertainty independently as well as simultaneously. It is sometimes challenging to distinguish between variability and parameter uncertainty in this context as both can involve the distributions of a random variable. The types of uncertainty include scenario, parameter, and model. More information on variability and uncertainty is provided in Chapter 2 of this handbook. The uncertainty and variability associated with the studies were evaluated based on the following criteria:

a) **Variability in the Population:** Studies were sought that characterized any variability within populations. The variability associated with the recommended exposure factors is described in Section 1.6. Higher confidence ratings were given to exposure factors that were based on studies where variability was well characterized.

b) **Uncertainty:** Studies were sought with minimal uncertainty in the data, which was judged by evaluating all the considerations listed above. Studies were preferred that identified uncertainties, such as those due to possible measurement error. Higher confidence ratings were given to exposure factors based on studies where uncertainty had been minimized.

5) *Evaluation and Review: The information or the procedures, measures, methods, or models are independently verified, validated, and peer reviewed.* Relevant factors that were considered included:

a) **Peer Review:** Studies selected were those from the peer-reviewed literature and final government reports. Unpublished and internal or interim reports were avoided, where possible. but were used in some cases to supplement information in published literature or government reports.

b) **Number and Agreement of Studies:** Higher confidence was placed on recommendations where data were available from more than one key study, and there was good agreement between studies.

1.6. APPROACH USED TO DEVELOP RECOMMENDATIONS FOR EXPOSURE FACTORS

As discussed above, the U.S. EPA first reviewed the literature pertaining to a factor and determined key studies. These key studies were used to derive recommendations for the values of each factor. The recommended values were derived solely from the U.S. EPA's interpretation of the available data. Different values may be appropriate for the user in consideration of policy, precedent, strategy, or other factors such as site-specific information. The U.S. EPA's procedure for developing recommendations was as follows:

1) *Study Review and Evaluation:* Key studies were evaluated in terms of both quality and relevance to specific populations (general U.S. population, age groups, sex, etc.). Section 1.5 describes the criteria for assessing the quality of studies.

2) *Selection of One versus Multiple Key Studies:* If only one study was classified as key for a particular factor, the mean value from that study was selected as the recommended central value for that population. If multiple key studies with reasonably equal quality, relevance, and study design information were available, a weighted mean (if appropriate, considering sample size and other statistical factors) of the studies was chosen as the recommended

mean value. Recommendations for upper percentiles, when multiple studies were available, were calculated as the mid-point of the range of upper percentile values of the studies for each age group where data were available. It is recognized that the mid-point of the range of upper percentiles may not provide the best estimate, but in the absence of raw data, more sophisticated analysis could not be performed.

3) *Assessing Variability:* The variability of the factor across the population is discussed. For recommended values, as well as for each of the studies on which the recommendations are based, variability was characterized in one or more of three ways: (1) as a table with various percentiles or ranges of values; (2) as analytical distributions with specified parameters; and/or (3) as a qualitative discussion. Analyses to fit standard or parametric distributions (e.g., normal, lognormal) to the exposure data have not been performed by the authors of this handbook, but have been reproduced as they were found in the literature. Recommendations on the use of these distributions were made where appropriate based on the adequacy of the supporting data. Table 1-1 presents the list of exposure factors and the way in which variability in the population has been characterized throughout this handbook (i.e., average, median, upper percentiles, multiple percentiles).

In providing recommendations for the various exposure factors, an attempt was made to present percentile values that are consistent with the exposure estimators defined in *Guidelines for Exposure Assessment* (U.S. EPA, 1992c) (i.e., mean, 50th, 90th, 95th, 98th, and 99.9^{th} percentiles). However, this was not always possible, because the data available were limited for some factors, or the authors of the study did not provide such information. It is important to note, however, that these percentiles were discussed in the guidelines within the context of risk descriptors and not individual exposure factors. For example, the guidelines state that the assessor may derive a high-end estimate of exposure by using maximum or near maximum values for one or more sensitive exposure factors, leaving others at their mean value. The term "upper percentile" is used throughout this handbook, and it is intended to represent values in the upper tail (i.e., between 90th and 99.9^{th} percentiles) of the distribution of values for a particular exposure factor. Tables providing summaries of recommendations at the beginning of each chapter generally present a mean and an upper percentile value. The 95th percentile was used as the upper percentile in these tables, if available, because it is the middle of the range between the 90th and 99.9^{th} percentiles. Other percentiles are presented, where available, in the tables at the end of the chapters. Users of the handbook should employ the exposure metric that is most appropriate for their particular situation.

4) *Assessing Uncertainty:* Uncertainties are discussed in terms of data limitations, the range of circumstances over which the estimates were (or were not) applicable, possible biases in the values themselves, a statement about parameter uncertainties (measurement error, sampling error), and model or scenario uncertainties if models or scenarios were used to derive the recommended value. A more detailed discussion of variability and uncertainty for exposure factors is presented in Chapter 2 of this handbook.

5) *Assigning Confidence Ratings:* Finally, the U.S. EPA assigned a confidence rating of *low, medium,* or *high* to each recommended value in each chapter. This qualitative rating is not intended to represent an uncertainty analysis; rather, it represents the U.S. EPA's judgment on the quality of the underlying data used to derive the recommendation. This judgment was made using the GAFs described in Section 1.5. Table 1-2 provides an adaptation of the GAFs, as they pertain to the confidence ratings for the exposure factor recommendations. Clearly, there is a continuum from *low to high*, and judgment was used to assign a rating to each factor. It is important to note that these confidence ratings are based on the strengths and limitations of the underlying data and not on how these data may be used in a particular exposure assessment.

The study elements listed in Table 1-2 do not have the same weight when arriving at the overall confidence rating for the various exposure factors. The relative weight of each of these elements for the various factors was subjective and based on the professional judgment of the authors of this handbook.

Also, the relative weights depend on the exposure factor of interest. For example, the adequacy of the data collection period may be more important when determining usual intake of foods in a population, but it is not as important for factors where long-term variability may be small, such as tap water intake. In the case of tap water intake, the currency of the data was a critical element in determining the final rating. In general, most studies ranked high with regard to "level of peer review," "accessibility," "focus on the factor of interest," and "data pertinent to the United States" because the U.S. EPA specifically sought studies for the handbook that met these criteria.

The confidence rating is also a reflection of the ease at which the exposure factor of interest could be measured. This is taken into consideration under the *soundness* criterion. For example, soil ingestion by children can be estimated by measuring, in feces, the levels of certain elements found in soil. Body weight, however, can be measured directly, and it is, therefore, a more reliable measurement than estimation of soil ingestion. The fact that soil ingestion is more difficult to measure than body weight is reflected in the overall confidence rating given to both of these factors. In general, the better the methodology used to measure the exposure factor, the higher the confidence in the value.

Some exposure factors recommendations may have different confidence ratings depending on the population of interest. For example a lower confidence rating may be noted for some age groups for which sample sizes are small. As another example, a lower confidence rating was assigned to the recommendations as they would apply to long-term chronic exposures versus acute exposures because of the short-term nature of the data collection period. To the extent possible, these caveats were noted in the confidence rating tables.

6) *Recommendation Tables:* The U.S. EPA developed a table at the beginning of each chapter that summarizes the recommended values for the relevant factor. Table ES-1 of the Executive Summary of this handbook summarizes the principal exposure factors addressed in this handbook and provides the confidence ratings for each exposure factor.

1.7. SUGGESTED REFERENCES FOR USE IN CONJUNCTION WITH THIS HANDBOOK

Many of the issues related to characterizing exposure from selected exposure pathways have been addressed in a number of existing U.S. EPA documents. Some of these provide guidance while others demonstrate various aspects of the exposure process. These include, but are not limited to, the following references listed in chronological order:

- *Methods for Assessing Exposure to Chemical Substances, Volumes 1–13* (U.S. EPA, 1983-1989);
- *Standard Scenarios for Estimating Exposure to Chemical Substances During Use of Consumer Products* (U.S. EPA, 1986b, c);
- *Selection Criteria for Mathematical Models Used in Exposure Assessments: Surface Water Models* (U.S. EPA, 1987b);
- *Selection Criteria for Mathematical Models Used in Exposure Assessments: Groundwater Models* (U.S. EPA, 1988);
- *Risk Assessment Guidance for Superfund, Volume I, Part A, Human Health Evaluation Manual* (U.S. EPA, 1989b);
- *Methodology for Assessing Health Risks Associated with Indirect Exposure to Combustor Emissions* (U.S. EPA, 1990);
- *Risk Assessment Guidance for Superfund, Volume I, Part B, Development of Preliminary Remediation Goals* (U.S. EPA, 1991a);
- *Risk Assessment Guidance for Superfund, Volume I, Part C, Risk Evaluation of Remedial Alternatives* (U.S. EPA, 1991b);
- *Guidelines for Exposure Assessment* (U.S. EPA, 1992c);
- *Dermal Exposure Assessment: Principles and Applications* (U.S. EPA, 1992a);
- *Soil Screening Guidance* (U.S. EPA, 1996b);
- *Series 875 Occupational and Residential Exposure Test Guidelines—Final Guidelines—Group A—Application Exposure Monitoring Test Guidelines* (U.S. EPA, 1996a);
- *Series 875 Occupational and Residential Exposure Test Guidelines—Group B—Post Application Exposure Monitoring Test Guidelines* (U.S. EPA, 1998);
- *Policy for Use of Probabilistic Analysis in Risk Assessment at the U.S. Environmental Protection Agency* (U.S. EPA, 1997c);

- *Guiding Principles for Monte Carlo Analysis* (U.S. EPA, 1997b);
- *Sociodemographic Data for Identifying Potentially Highly Exposed Populations* (U.S. EPA, 1999);
- *Options for Development of Parametric Probability Distributions for Exposure Factors* (U.S. EPA, 2000a);
- *Risk Assessment Guidance for Superfund, Volume I, Part D, Standardized Planning, Reporting, and Review of Superfund Risk Assessments* (U.S. EPA, 2001b);
- *Risk Assessment Guidance for Superfund Volume III, Part A, Process for Conducting Probabilistic Risk Assessments* (U.S. EPA, 2001c)
- *Framework for Cumulative Risk Assessment* (U.S. EPA, 2003b);
- *Example Exposure Scenarios* (U.S. EPA, 2004a);
- *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds National Academy Sciences Review Draft* (U.S. EPA, 2003a);
- *Risk Assessment Guidance for Superfund, Volume I, Part E, Supplemental Guidance for Dermal Risk Assessment* (U.S. EPA, 2004b);
- *Cancer Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005c);
- *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005e);
- *Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants* (U.S. EPA, 2005b);
- *Human Health Risk Assessment Protocol for Hazardous Waste Combustion Facilities* (U.S. EPA, 2005d);
- *Aging and Toxic Response: Issues Relevant to Risk Assessment* (U.S. EPA, 2005a);
- *A Framework for Assessing Health Risk of Environmental Exposures to Children* (U.S. EPA, 2006b);
- *Dermal Exposure Assessment: A Summary of EPA Approaches* (U.S. EPA, 2007b);
- *Child-Specific Exposure Factors Handbook* (U.S. EPA, 2008a);
- *Concepts, Methods, and Data Sources For Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document* (U.S. EPA, 2007a);

- *Physiological Parameters Database for Older Adults (Beta 1.1)* (U.S. EPA, 2008b);
- *Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual Part F, Supplemental Guidance for Inhalation Risk Assessment* (U.S. EPA, 2009b);
- *Draft Technical Guidelines Standard Operating Procedures for Residential Pesticide Exposure Assessment* (U.S. EPA, 2009a);
- *Stochastic Human Exposure and Dose Simulation (SHEDS)-Multimedia. Details of SHEDS-Multimedia Version 3: ORD/NERL's Model to Estimate Aggregate and Cumulative Exposures to Chemicals* (U.S. EPA, 2010); and
- *Recommended Use of Body Weight$^{3/4}$ (BW$^{3/4}$) as the Default Method in Derivation of the Oral Reference Dose (RfD)* (U.S. EPA, 2011).

These documents may serve as valuable information resources to assist in the assessment of exposure. Refer to them for more detailed discussion.

1.8. THE USE OF AGE GROUPINGS WHEN ASSESSING EXPOSURE

When this handbook was published in 1997, no specific guidance existed with regard to which age groupings should be used when assessing children's exposure. Age groupings varied from case to case and among Program Offices within the U.S. EPA. They depended on availability of data and were often based on professional judgment. More recently, the U.S. EPA has established a consistent set of age groupings and published guidance on this topic (U.S. EPA, 2005b). This revision of the handbook attempts to present data in a manner consistent with the U.S. EPA's recommended set of age groupings for children. The presentation of data for these fine age categories does not necessarily mean that every age category needs to be the subject of a particular assessment. It will depend on the objectives of the assessment and communications with toxicologists to identify the critical windows of susceptibility.

The development of standardized age bins for children was the subject of discussion in a 2000 workshop sponsored by the U.S. EPA Risk Assessment Forum. The workshop was titled *Issues Associated with Considering Developmental Changes in Behavior and Anatomy When Assessing Exposure to Children* (U.S. EPA, 2000b). The purpose of this

workshop was to gain insight and input into factors that need to be considered when developing standardized age bins and to identify future research necessary to accomplish these goals.

Based upon consideration of the findings of the technical workshop, as well as analysis of available data, U.S. EPA developed guidance that established a set of recommended age groups for development of exposure factors for children entitled *Guidance for Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants* (U.S. EPA, 2005b). This revision of the handbook for individuals <21 years of age presents exposure factors data in a manner consistent with U.S. EPA's recommended set of childhood age groupings. The recommended age groups (U.S. EPA, 2005b) are as follows:

> Birth to <1 month
> 1 to <3 months
> 3 to <6 months
> 6 to <12 months
> 1 to <2 years
> 2 to <3 years
> 3 to <6 years
> 6 to <11 years
> 11 to <16 years
> 16 to <21 years

1.9. CONSIDERING LIFE STAGE WHEN CALCULATING EXPOSURE AND RISK

In recent years, there has been an increased concern regarding the potential impact of environmental exposures to children and other susceptible populations such as older adults and pregnant/lactating women. As a result, the U.S. EPA and others have developed policy and guidance and undertaken research to better incorporate life stage data into human health risk assessment (Brown et al., 2008). The *Child-Specific Exposure Factors Handbook* was published in 2008 to address the need to characterize children's exposures at various life stages (U.S. EPA, 2008a). Children are of special concern because (1) they consume more of certain foods and water per unit of body weight than adults; (2) they have a higher ratio of body surface area to volume than adults; and (3) they experience important, rapid changes in behavior and physiology that may lead to differences in exposure (Moya et al., 2004). Many studies have shown that young children can be exposed to various contaminants, including

pesticides, during normal oral exploration of their environment (i.e., hand-to-mouth behavior) and by touching floors, surfaces, and objects such as toys (Garry, 2004; Eskenazi et al., 1999; Lewis et al., 1999; Nishioka et al., 1999; Gurunathan et al., 1998). Dust and tracked-in soil accumulate in carpets, where young children spend a significant amount of time (Lewis et al., 1999). Children living in agricultural areas may experience higher exposures to pesticides than do other children (Curwin et al., 2007). They may play in nearby fields or be exposed via consumption of contaminated human milk from their farmworker mothers (Eskenazi et al., 1999).

In terms of risk, children may also differ from adults in their vulnerability to environmental pollutants because of toxicodynamic differences (e.g., when exposures occur during periods of enhanced susceptibility) and/or toxicokinetic differences (i.e., differences in absorption, metabolism, and excretion) (U.S. EPA, 2000b). The immaturity of metabolic enzyme systems and clearance mechanisms in young children can result in longer half-lives of environmental contaminants (Clewell et al., 2004; Ginsberg et al., 2002). The cellular immaturity of children and the ongoing growth processes account for elevated risk (American Academy of Pediatrics, 1997). Toxic chemicals in the environment can cause neurodevelopmental disabilities, and the developing brain can be particularly sensitive to environmental contaminants. For example, elevated blood lead levels and prenatal exposures to even relatively low levels of lead can result in behavior disorders and reductions of intellectual function in children (Landrigan et al., 2005). Exposure to high levels of methylmercury can result in developmental disabilities (e.g., intellectual deficiency, speech disorders, and sensory disturbances) among children (Myers and Davidson, 2000). Other authors have described the importance of exposure timing (i.e., pre-conceptional, prenatal, and postnatal) and how it affects the outcomes observed (Selevan et al., 2000). Exposures during these critical windows of development and age-specific behaviors and physiological factors can lead to differences in response (Makri et al., 2004). Fetal exposures can occur from the mobilization of chemicals of maternal body burden and transfer of those chemicals across the placenta (Makri et al., 2004). Absorption through the gastrointestinal tract is more efficient in neonates and infants, making ingestion exposures a significant route of exposure during the first year of age (Makri et al., 2004).

It has also been suggested that higher levels of exposure to indoor air pollution and allergens among inner-city children compared to non-inner-city

children may explain the difference in asthma levels between these two groups (Breysse et al., 2005). With respect to contaminants that are carcinogenic via a mutagenic mode of action (MOA), the U.S. EPA has found that childhood is a particularly sensitive period of development in which cancer potencies per year of exposure can be an order of magnitude higher than during adulthood (U.S. EPA, 2005e).

A framework for considering life stages in human health risk assessments was developed by the U.S. EPA in the report entitled *A Framework for Assessing Health Risks of Environmental Exposures to Children* (U.S. EPA, 2006b). Life stages are defined as "temporal stages (or intervals) of life that have distinct anatomical, physiological, behavioral, and/or functional characteristics that contribute to potential differences in environmental exposures" (Brown et al., 2008). One way to understand the differential exposures among life stages is to study the data using age binning or age groups as it is the recommendation for childhood exposures. Although the framework discusses the importance of incorporating life stages in the evaluation of risks to children, the approach can also be applied to other life stages that may have their own unique susceptibilities. For example, older individuals may experience differential exposures and risks to environmental contaminants due to biological changes that occur during aging, disease status, drug interactions, different exposure patterns, and activities. More information on the toxicokinetic and toxicodynamic impact of environmental agents in older adults can be found in U.S. EPA's document entitled *Aging and Toxic Response: Issues Relevant to Risk Assessment* (U.S. EPA, 2005a). The need to better characterize differential exposures of the older adult population to environmental agents was recognized at the U.S. EPA's workshop on the development of exposure factors for the aging (U.S. EPA, 2007c). A panel of experts in the fields of gerontology, physiology, exposure assessment, risk assessment, and behavioral science discussed existing data, data gaps, and current relevant research on the behavior and physiology of older adults, as well as practical considerations of the utility of developing an exposure factors handbook for the aging (U.S. EPA, 2007c). Pregnant and lactating women may also be a life stage of concern due to physiological changes during pregnancy and lactation. For example, lead is mobilized from the maternal skeleton during pregnancy and the postpartum period, increasing the chances for fetal lead exposure (Gulson et al., 1999).

The U.S. EPA encourages the consideration of all life stages and endpoints to ensure that vulnerabilities during specific time periods are taken into account (Brown et al., 2008). Although the importance of assessing risks from environmental exposures to all susceptible populations is recognized, most of the guidance developed thus far relates to children. Furthermore, it is recognized that there is a lack of dose-response data to evaluate differential responses at various life stages (e.g., age groups, pregnant/lactating mothers, older populations). A key component of U.S. EPA's *Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants* (U.S. EPA, 2005b) involves the need to sum age-specific exposures across time when assessing long-term exposure, as well as integrating these age-specific exposures with age-specific differences in toxic potency in those cases where information exists to describe such differences: an example is carcinogens that act via a mutagenic mode of action [*Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* – (U.S. EPA, 2005e)]. When assessing chronic risks (i.e., exposures greater than 10% of human lifespan), rather than assuming a constant level of exposure for 70 years (usually consistent with an adult level of exposure), the Agency is now recommending that assessors calculate chronic exposures by summing time-weighted exposures that occur at each life stage; this handbook provides data arrayed by childhood age in order to follow this new guidance (U.S. EPA, 2005e). This approach is expected to increase the accuracy of risk assessments, because it will take into account life stage differences in exposure. Depending on whether body-weight-adjusted childhood exposures are either smaller or larger compared to those for adults, calculated risks could either decrease or increase when compared with the historical approach of assuming a lifetime of a constant adult level of exposure.

The *Supplemental Guidance* report also recommended that in those cases where age-related differences in toxicity were also found to occur, differences in both toxicity and exposure would need to be integrated across all relevant age intervals (U.S. EPA, 2005e). This guidance describes such a case for carcinogens that act via a mutagenic mode of action, where age dependent adjustments factors (ADAFs) of 10× and 3× are recommended for children ages birth to <2 years, and 2 to <16 years, respectively, when there is exposure during those years, and available data are insufficient to derive chemical-specific adjustment factors.

Table 1-3, along with Chapter 6 of the *Supplemental Guidance* (U.S. EPA, 2005e) report, have been developed to help the reader understand

how to use the new sets of exposure and potency age groupings when calculating risk through the integration of life stage specific changes in exposure and potency for mutagenic carcinogens.

Thus, Table 1-3 presents Lifetime Cancer Risk (for a population with average life expectancy of 70 years) = $\sum$ (Exposure $\times$ Duration/70 years $\times$ Potency $\times$ ADAF) summed across all the age groups. This is a departure from the way cancer risks have historically been calculated based upon the premise that risk is proportional to the daily average of the long-term adult dose.

1.10.   FUNDAMENTAL PRINCIPLES OF EXPOSURE ASSESSMENT

An exposure assessment is the "process of estimating or measuring the magnitude, frequency, and duration of exposure to an agent, along with the number and characteristics of the population exposed" (Zartarian et al., 2007). The definition of exposure as used by the International Program on Chemical Safety (WHO, 2001) is the "contact of an organism with a chemical or physical agent, quantified as the amount of chemical available at the exchange boundaries of the organism and available for absorption." The term "agent" refers to a chemical, biological, or physical entity that contacts a target. The "target" refers to any physical, biological, or ecological object exposed to an agent. In the case of human exposures, the contact occurs with the visible exterior of a person (i.e., target) such as the skin, and openings such as the mouth, nostrils, and lesions. The process by which an agent crosses an outer exposure surface of a target without passing an absorption barrier (i.e., through ingestion or inhalation) is called an intake. The resulting dose is the intake dose. The intake dose is sometimes referred to in the literature as the administered dose or potential dose.

The terms "exposure" and "dose" are very closely related and, therefore, are often confused (Zartarian et al., 2007). Dose is the amount of agent that enters a target in a specified period of time after crossing a contact boundary. An exposure does not necessarily leads to a dose. However, there can be no dose without a corresponding exposure (Zartarian et al., 2007). Figure 1-1 illustrates the relationship between exposure and dose.
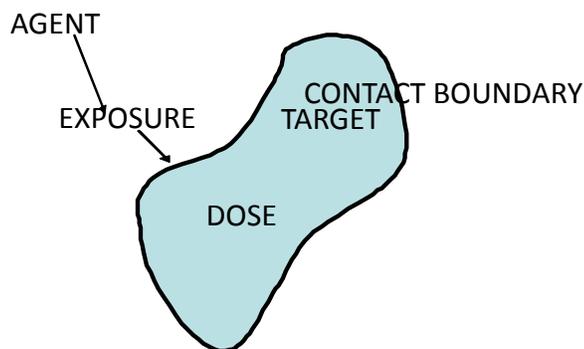
Figure 1-1. Conceptual Drawing of Exposure and Dose Relationship (Zartarian et al., 2007).

In other words, the process of an agent entering the body can be described in two steps: contact (exposure) followed by entry (crossing the boundary). In the context of environmental risk assessment, risk to an individual or population can be represented as a continuum from the source through exposure to dose to effect as shown in Figure 1-2 (Ott, 2007; WHO, 2006; U.S. EPA, 2003c). The process begins with a chemical or agent released from a source into the environment. Once in the environment, the agent can be transformed and transported through the environment via air, water, soil, dust, and diet (i.e., exposure pathway). Fate and transport mechanisms result in various chemical concentrations with which individuals may come in contact. Individuals encounter the agent either through inhalation, ingestion, or skin/eye contact (i.e., exposure route). The individual's activity patterns as well as the concentration of the agent will determine the magnitude, frequency, and duration of the exposure. The exposure becomes an absorbed dose when the agent crosses an absorption barrier (e.g., skin, lungs, gut). Other terms used in the literature to refer to absorbed dose include internal dose, bioavailable dose, delivered dose, applied dose, active dose, and biologically effective dose (Zartarian et al., 2007). When an agent or its metabolites interact with a target tissue, it becomes a target tissue dose, which may lead to an adverse health outcome. The text under the boxes in Figure 1-2 indicates the specific information that may be needed to characterize each box.

This approach has been used historically in exposure assessments and exposure modeling. It is usually referred to as source-to-dose approach. In recent years, person-oriented approaches and models have gained popularity. This approach is aimed at accounting for cumulative and aggregate exposures to individuals (Georgopoulos, 2008; Price et al.,

2003a). The person-oriented approach can also take advantage of information about the individual's susceptibility to environmental factors (e.g., genetic differences) (Georgopoulos, 2008).

There are three approaches to calculate exposures: (1) the point-of-contact approach, (2) the scenario evaluation approach, and (3) the dose reconstruction approach (U.S. EPA, 1992c). The data presented in this handbook are generally useful for evaluating exposures using the scenario approach. There are advantages and disadvantages associated with each approach. Although it is not the purpose of this handbook to provide guidance on how to conduct an exposure assessment, a brief description of the approaches is provided below.

The point-of-contact approach, or direct approach, involves measurements of chemical concentrations at the point where exposure occurs (i.e., at the interface between the person and the environment). This chemical concentration is coupled with information on the length of contact with each chemical to calculate exposure. The scenario evaluation approach, or the indirect approach, utilizes data on chemical concentration, frequency, and duration of exposure as well as information on the behaviors and characteristics of the exposed life stage. The third approach, dose reconstruction, allows exposure to be estimated from dose, which can be reconstructed through the measurement of biomarkers of exposure. A biomarker of exposure is a chemical, its metabolite, or the product of an interaction between a chemical and some target molecule or cell that is measured in a compartment in an organism (NRC, 2006). Biomonitoring is becoming a tool for identifying, controlling, and preventing human exposures to environmental chemicals (NRC, 2006). For example, blood lead concentrations and the associated health effects were used by the U.S. EPA in its efforts to reduce exposure to lead in gasoline. The Centers for Disease Control and Prevention conducts biomonitoring studies to help identify chemicals that are both present in the environment and in human tissues (NRC, 2006). Biomonitoring studies also assist public health officials in studying distributions of exposure in a population and how they change overtime. Biomonitoring data can be converted to exposure using pharmacokinetic modeling (NRC, 2006). Although biomonitoring can be a powerful tool, interpretation of the data is difficult. Unlike the other two approaches, biomonitoring provides information on internal doses integrated across environmental pathways and media. Interpretation of these data requires knowledge and understanding of how the chemicals are absorbed, excreted, and metabolized in

the biological system, as well as the properties of the chemicals and their metabolites (NRC, 2006). The interpretation of biomarker data can be further improved by the development of other cellular and molecular approaches to include advances in genomics, proteomics, and other approaches that make use of molecular-environmental interactions (Lioy et al., 2005). Physiological parameters can also vary with life stage, age, sex, and other demographic information (Price et al., 2003b). Physiologic and metabolic factors and how they vary with life stage have been the subject of recent research. Pharmacokinetic models are frequently developed from data obtained from young adults. Therapeutic drugs have been used as surrogates to study pharmacokinetic differences in fetuses, children, and adults (Ginsberg et al., 2004). Specific considerations of susceptibilities for other populations (e.g., children, older adults) require knowledge of the physiological parameters that most influence the disposition of the chemicals in the body (Thompson et al., 2009). Physiological parameters include alveolar ventilation, cardiac output, organ and tissue weights and volumes, blood flows to organs and tissues, clearance parameters, and body composition (Thompson et al., 2009). Price et al. (2003b) developed a tool for capturing the correlation between organs and tissue and compartment volumes, blood flows, body weight, sex, and other demographic information. A database that records key, age-specific pharmacokinetic model inputs for healthy older adults and for older adults with conditions such as diabetes, chronic obstructive pulmonary disease, obesity, heart disease, and renal disease has been developed by the U.S. EPA (Thompson et al., 2009; U.S. EPA, 2008b).

Computational exposure models can play an important role in estimating exposures to environmental chemicals (Sheldon and Cohen Hubal, 2009). In general, these models combine measurements of the concentration of the chemical agent in the environment (e.g., air, water, soil, food) with information about the individual's activity patterns to estimate exposure (WHO, 2005). Several models have been developed and may be used to support risk management decisions. For example, the U.S. EPA SHEDS model is a probabilistic model that simulates daily activities to predict distributions of daily exposures in a population (U.S. EPA, 2010). Other models such as the Modeling Environment for Total Risk Studies incorporates and expands the approach used by SHEDS and considers multiple routes of exposure (Georgopoulos and Lioy, 2006).

1.10.1. Exposure and Dose Equations

Exposure can be quantified by multiplying the concentration of an agent times the duration of the contact. Exposure can be instantaneous when the contact between an agent and a target occurs at a single point in time and space (Zartarian et al., 2007). The summation of instantaneous exposures over the exposure duration is called the time-integrated exposure (Zartarian et al., 2007). Equation 1-1 shows the time-integrated exposure.

$$E = \int_{t_1}^{t_2} C(t)dt \qquad \text{(Eqn. 1-1)}$$

where:

E = Time-integrated exposure (mass/volume),

$t_2 - t_1$ = Exposure duration (ED) (time), and

C = Exposure concentration as a function of time (mass/volume).

Dividing the time-integrated exposure by the exposure duration, results in the time-averaged exposure (Zartarian et al., 2007).

Dose can be classified as an intake dose or an absorbed dose (U.S. EPA, 1992c). Starting with a general integral equation for exposure, several dose equations can be derived depending upon boundary assumptions. One of the more useful of these derived equations is the average daily dose (ADD). The ADD, which is used for many non-cancer effects, averages exposures or doses over the period of time exposure occurred. The ADD can be calculated by averaging the intake dose over body weight and an averaging time as shown in Equations 1-2 and 1-3.

$$ADD = \frac{Intake\ Dose}{Body\ Weight\ \times\ Averaging\ Time} \qquad \text{(Eqn. 1-2)}$$

The exposure can be expressed as follows:

$$\text{Intake Dose} = C \times IR \times ED \qquad \text{(Eqn. 1-3)}$$

where:

C = Concentration of the Agent (mass/volume),

IR = Intake Rate (mass/time), and

ED = Exposure Duration (time).

Concentration of the agent is the mass of the agent in the medium (air, food, soil, etc.) per unit volume contacting the body and has units of mass/volume or mass/mass.

The intake rate refers to the rates of inhalation, ingestion, and dermal contact, depending on the route of exposure. For ingestion, the intake rate is simply the amount of contaminated food ingested by an individual during some specific time period (units of mass/time). Much of this handbook is devoted to rates of ingestion for some broad classes of food. For inhalation, the intake rate is that at which contaminated air is inhaled. Factors presented in this handbook that affect dermal exposure are skin surface area and estimates of the amount of solids that adheres to the skin, film thickness of liquids to skin, transfer of residues, and skin thickness. It is important to note that there are other key factors in the calculation of dermal exposures that are not covered in this handbook (e.g., chemical-specific absorption factors).

The exposure duration is the length of time of contact with an agent. For example, the length of time a person lives in an area, frequency of bathing, time spent indoors versus outdoors, and in various microenvironments, all affect the exposure duration. Chapter 16, Activity Factors, gives some examples of population behavior and macro and micro activities that may be useful for estimating exposure durations.

When the above parameter values IR and ED remain constant over time, they are substituted directly into the dose equation. When they change with time, a summation approach is needed to calculate dose. In either case, the exposure duration is the length of time exposure occurs at the concentration and the intake rate specified by the other parameters in the equation.

Note that the advent of childhood age groupings means that separate ADDs should be calculated for each age group considered. Chronic exposures can then be calculated by summing across each life stage-specific ADD.

Cancer risks have traditionally been calculated in those cases where a linear non-threshold model is assumed, in terms of lifetime probabilities by utilizing dose values presented in terms of lifetime ADDs (LADDs). The LADD takes the form of Equation 1-2, with lifetime replacing averaging time. While the use of LADDs may be appropriate when developing screening-level estimates of cancer risk, the U.S. EPA recommends that risks should be calculated by integrating exposures or risks throughout all life stages (U.S. EPA, 1992c).

For some types of analyses, dose can be expressed as a total amount (with units of mass, e.g., mg) or as a dose rate in terms of mass/time (e.g., mg/day), or as a rate normalized to body mass (e.g., with units of mg of chemical per kg of body weight per day [mg/kg-day]). The LADD is usually expressed in terms of mg/kg-day or other mass/mass-time units.

In most cases (inhalation and ingestion exposures), the dose-response parameters for carcinogenic risks have been adjusted for the difference in absorption across body barriers between humans and the experimental animals used to derive such parameters. Therefore, the exposure assessment in these cases is based on the intake dose, with no explicit correction for the fraction absorbed. However, the exposure assessor needs to make such an adjustment when calculating dermal exposure and in other specific cases when current information indicates that the human absorption factor used in the derivation of the dose-response factor is inappropriate.

For carcinogens, the duration of a lifetime has traditionally been assigned the nominal value of 70 years as a reasonable approximation. For dose estimates to be used for assessments other than carcinogenic risk, various averaging periods have been used. For acute exposures, the doses are usually averaged over a day or a single event. For non-chronic non-cancer effects, the time period used is the actual period of exposure (exposure duration). The objective in selecting the exposure averaging time is to express the dose in a way that can be combined with the dose-response relationship to calculate risk.

The body weight to be used in Equation 1-2 depends on the units of the exposure data presented in this handbook. For example, for food ingestion, the body weights of the surveyed populations were known in the USDA and NHANES surveys, and they were explicitly factored into the food intake data in order to calculate the intake as g/kg body weight-day. In this case, the body weight has already been included in the "intake rate" term in Equation 1-3, and the exposure assessor does not need to explicitly include body weight.

The units of intake in this handbook for the incidental ingestion of soil and dust are not normalized to body weight. In this case, the exposure assessor will need to use (in Equation 1-2) the average weight of the exposed population during the time when the exposure actually occurs. When making body-weight assumptions, care must be taken that the values used for the population parameters in the dose-response analysis are consistent with the population parameters used in the exposure analysis. Intraspecies adjustments based on life stage can be made using a correction factor (CF) (U.S. EPA, 2011, 2006b). Appendix 1A of this chapter discusses these adjustments in more detail. Some of the parameters (primarily concentrations) used in estimating exposure are exclusively site specific, and, therefore, default recommendations should not be used. It should be noted that body weight is correlated with food consumption rates, body surface area, and inhalation rates (for more information, see Chapters 6, 7, 9, 10, 11, 12, 13, and 14).

The link between the intake rate value and the exposure duration value is a common source of confusion in defining exposure scenarios. It is important to define the duration estimate so that it is consistent with the intake rate:

- The intake rate can be based on an individual event (e.g., serving size per event). The duration should be based on the number of events or, in this case, meals.
- The intake rate also can be based on a long-term average, such as 10 g/day. In this case, the duration should be based on the total time interval over which the exposure occurs.

The objective is to define the terms so that, when multiplied, they give the appropriate estimate of mass of agent contacted. This can be accomplished by basing the intake rate on either a long-term average (chronic exposure) or an event (acute exposure) basis, as long as the duration value is selected appropriately.

Inhalation dosimetry is employed to derive the human equivalent exposure concentrations on which inhalation unit risks (IURs), and reference concentrations (RfCs), are based (U.S. EPA, 1994). U.S. EPA has traditionally approximated children's respiratory exposure by using adult values, although a recent review (Ginsberg et al., 2005) concluded that there may be some cases where young children's greater inhalation rate per body weight or pulmonary surface area as compared to adults can result in greater exposures than adults. The implications of this difference for inhalation dosimetry and children's risk assessment were discussed at a peer involvement workshop hosted by the U.S. EPA in 2006 (Foos et al., 2008).

Consideration of life stage-particular physiological characteristics in the dosimetry analysis may result in a refinement to the human equivalent

concentration (HEC) to ensure relevance in risk assessment across life stages, or might conceivably conclude with multiple HECs, and corresponding IUR values (e.g., separate for childhood and adulthood) (U.S. EPA, 2005e). The RfC methodology, which is described in *Methods for Derivation of Inhalation Reference Concentrations and Applications of Inhalation Dosimetry* (U.S. EPA, 1994), allows the user to incorporate population-specific assumptions into the models. Refer to U.S. EPA guidance (U.S. EPA, 1994) on how to make these adjustments.

There are no specific exposure factor assumptions in the derivation of RfDs for susceptible populations. With regard to childhood exposures for a susceptible population, for example, the assessment of the potential for adverse health effects in infants and children is part of the overall hazard and dose-response assessment for a chemical. Available data pertinent to children's health risks are evaluated along with data on adults and the no-observed-adverse-effect level (NOAEL) or benchmark dose (BMD) for the most sensitive critical effect(s), based on consideration of all health effects. By doing this, protection of the health of children will be considered along with that of other sensitive populations. In some cases, it is appropriate to evaluate the potential hazard to a susceptible population (e.g., children) separately from the assessment for the general population or other population groups. For more information regarding life stage-specific considerations for assessing children exposures, refer to the U.S. EPA report entitled *Framework for Assessing Health Risk of Environmental Exposures to Children* (U.S. EPA, 2006b).

1.10.2. Use of Exposure Factors Data in Probabilistic Analyses

Probabilistic risk assessment provides a range and likelihood estimate of risk rather than a single point estimate. It is a tool that can provide additional information to risk managers to improve decision making. Although this handbook is not intended to provide complete guidance on the use of Monte Carlo and other probabilistic analyses, some of the data in this handbook may be appropriate for use in probabilistic assessments. More detailed information on treating variability and uncertainty is discussed in Chapter 2 of this handbook. The use of Monte Carlo or other probabilistic analysis requires characterization of the variability of exposure factors and requires the selection of distributions or histograms for the input parameters of the dose equations presented in Section 1.10.1. The following

suggestions are provided for consideration when using such techniques:

- The exposure assessor should only consider using probabilistic analysis when there are credible distribution data (or ranges) for the factor under consideration. Even if these distributions are known, it may not be necessary to apply this technique. For example, if only average exposure values are needed, these can often be computed accurately by using average values for each of the input parameters unless a non-linear model is used. Generally, exposure assessments follow a tiered approach to ensure the efficient use of resources. They may start with very simple techniques and move to more sophisticated models. The level of assessment needed can be determined initially during the problem formulation. There is also a tradeoff between the level of sophistication and the need to make timely decisions (NRC, 2009). Probabilistic analysis may not be necessary when conducting assessments for the first tier, which is typically done for screening purposes, i.e., to determine if unimportant pathways can be eliminated. In this case, bounding estimates can be calculated using maximum or near maximum values for each of the input parameters. Alternatively, the assessor may use the maximum values for those parameters that have the greatest variance.

- The selection of distributions can be highly site-specific and dependent on the purpose of the assessment. In some cases, the selection of distributions is driven by specific legislation. It will always involve some degree of judgment. Distributions derived from national data may not represent local conditions. Also, distributions may be representative of some age groups, but not representative when finer age categories are used. The assessor should evaluate the distributional data to ensure that it is representative of the population that needs to be characterized. In cases where site-specific data are available, the assessor may need to evaluate their quality and applicability. The assessor may decide to use distributional data drawn from the national or other surrogate population. In this case, it is important that the assessor address the extent to which local conditions may differ from the surrogate data.

- It is also important to consider the independence/dependence of variables and data used in a simulation. For example, it may

be reasonable to assume that ingestion rate and contaminant concentration in foods are independent variables, but ingestion rate and body weight may or may not be independent.

In addition to a qualitative statement of uncertainty, the representativeness assumption should be appropriately addressed as part of a sensitivity analysis. Distribution functions used in probabilistic analysis may be derived by fitting an appropriate function to empirical data. In doing this, it should be recognized that in the lower and upper tails of the distribution, the data are scarce, so that several functions, with radically different shapes in the extreme tails, may be consistent with the data. To avoid introducing errors into the analysis by the arbitrary choice of an inappropriate function, several techniques can be used. One technique is to avoid the problem by using the empirical data themselves rather than an analytic function. Another is to do separate analyses with several functions that have adequate fit but form upper and lower bounds to the empirical data. A third way is to use truncated analytical distributions. Judgment must be used in choosing the appropriate goodness-of-fit test.

Information on the theoretical basis for fitting distributions can be found in a standard statistics text, [e.g., Gilbert (1987), among others]. Off-the-shelf computer software can be used to statistically determine the distributions that fit the data. Other software tools are available to identify outliers and for conducting Monte Carlo simulations.

If only a range of values is known for an exposure factor, the assessor has several options. These options include:

- keep that variable constant at its central value;
- assume several values within the range of values for the exposure factor;
- calculate a point estimate(s) instead of using probabilistic analysis; and
- assume a distribution. (The rationale for the selection of a distribution should be discussed at length.) The effects of selecting a different, but equally probable distribution should be discussed. There are, however, cases where assuming a distribution may introduce considerable amount of uncertainty. These include:
  o data are missing or very limited for a key parameter;
  o data were collected over a short time period and may not represent long-term

trends (the respondent's usual behavior)— examples include food consumption surveys; activity pattern data;
  o data are not representative of the population of interest because sample size was small or the population studied was selected from a local area and was, therefore, not representative of the area of interest; for example, soil ingestion by children; and
  o ranges for a key variable are uncertain due to experimental error or other limitations in the study design or methodology; for example, soil ingestion by children.

1.11. AGGREGATE AND CUMULATIVE EXPOSURES

The U.S. EPA recognizes that individuals may be exposed to mixtures of chemicals both indoors and outdoors through more than one pathway. New directions in risk assessments in the U.S. EPA put more emphasis on total exposures via multiple pathways (U.S. EPA, 2007a, 2003c). Assessments that evaluate a single agent or stressor across multiple routes are not considered cumulative risk assessments. These are defined by the Food Quality Protection Act as aggregate risk assessments and can provide useful information to cumulative assessments (U.S. EPA, 2003c). Concepts and considerations to conduct aggregate risk assessments are provided in the U.S. EPA document entitled *General Principles for Performing Aggregate Exposure and Risk Assessments* (U.S. EPA, 2001a).

Cumulative exposure is defined as the exposure to multiple agents or stressors via multiple routes. In the context of risk assessment, it means that risks from multiple routes and agents need to be combined, not necessarily added (U.S. EPA, 2003b). Analysis needs to be conducted on how the various agents and stressors interact (U.S. EPA, 2003b).

In order to achieve effective risk assessment and risk management decisions, all media and routes of exposure should be assessed (NRC, 2009, 1991). Over the last several years, the U.S. EPA has developed a methodology for assessing risk from multiple chemicals (U.S. EPA, 2000c, 1986a). For more information, refer to the U.S. EPA's Framework for Cumulative Risk Assessment (U.S. EPA, 2003b). The recent report by the NAS also recommends the development of approaches to incorporate the interactions between chemical and non-chemical stressors (NRC, 2009).

1.12. ORGANIZATION OF THE HANDBOOK

All the chapters of this handbook have been organized in a similar fashion. An introduction is provided that discusses some general background information about the exposure factor. This discussion is followed by the recommendations for that exposure factor including summary tables of the recommendations and confidence ratings. The goal of the summary tables is to present the data in a simplified fashion by providing mean and upper percentile estimates and referring the reader to more detailed tables with more percentile estimates or other demographic information (e.g., sex) at the end of the chapter. Because of the large number of tables in this handbook, tables that include information other than the recommendations and confidence ratings are presented at the end of each chapter, before the appendices, if any. Following the recommendations, the key studies are summarized. Relevant data on the exposure factor are also provided. These data are presented to provide the reader with added perspective on the current state-of-knowledge pertaining to the exposure factor of interest. Summaries of the key and relevant studies include discussions about their strengths and limitations. Note that because the studies often were performed for reasons unrelated to developing the factor of interest, the attributes that were characterized as limitations might not be limitations when viewed in the context of the study's original purpose.

The handbook is organized as follows:

Chapter 1	Introduction—includes discussions about general concepts in exposure assessments as well as the purpose, scope, and contents of the handbook.
Chapter 2	Variability and Uncertainty—provides a brief overview of the concepts of variability and uncertainty and directs the reader to other references for more in-depth information.
Chapter 3	Ingestion of Water and Other Select Liquids—provides information on drinking water consumption and data on intake of select liquids for the general population and various demographic groups; also provides data on intake of water while swimming.
Chapter 4	Non-dietary Ingestion—presents data on mouthing behavior necessary to estimate non-dietary exposures.
Chapter 5	Soil and Dust Ingestion—provides information on soil and dust ingestion for both adults and children.
Chapter 6	Inhalation Rates—presents data on average daily inhalation rates and activity-specific inhalation rates for the general population and various demographic groups.
Chapter 7	Dermal Exposure Factors—presents information on body surface area and solids adherence to the skin, as well as data on other non-chemical-specific factors that may affect dermal exposure.
Chapter 8	Body Weight—provides data on body weight for the general population and various demographic groups.
Chapter 9	Intake of Fruits and Vegetables—provides information on total fruit and vegetable consumption as well as intake of individual fruits and vegetables for the general population and various demographic groups.
Chapter 10	Intake of Fish and Shellfish—provides information on fish consumption for the general population, recreational freshwater and marine populations, and various demographic groups.
Chapter 11	Intake of Meats, Dairy Products, and Fats—provides information on meat, dairy products, and fats consumption for the general population and various demographic groups.
Chapter 12	Intake of Grain Products—provides information on grain consumption for the general population and various demographic groups.
Chapter 13	Intake of Home-produced Foods—provides information on home-produced food consumption for the general population and various demographic groups.
Chapter 14	Total Food Intake—provides information on total food consumption for the general population and various demographic groups; information on the composition of the diet is also provided.

Figure 1-3 provides a schematic diagram that shows the linkages of a select number of exposure pathways with the exposure factors presented in this handbook and the corresponding exposure routes. Figure 1-4 provides a roadmap to assist users of this handbook in locating recommended values and confidence ratings for the various exposure factors presented in these chapters.

1.13.   REFERENCES FOR CHAPTER 1

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Table 1-1. Availability of Various Exposure Metrics in Exposure Factors Data					
Exposure Factors	Chapter	Average	Median	Upper Percentile	Multiple Percentiles
Ingestion of water and other select liquids (Chapter 3)	3	✓	✓	✓	✓
Non-dietary ingestion	4	✓	✓	✓	✓
Soil and dust ingestion	5	✓		✓[a]	
Inhalation rate	6	✓	✓	✓	✓
Surface area	7	✓	✓	✓	✓
Soil adherence	7	✓			
Body weight	8	✓	✓	✓	✓
Intake of fruits and vegetables	9	✓	✓	✓	✓
Intake of fish and shellfish	10	✓	✓	✓	✓
Intake of meats, dairy products, and fats	11	✓	✓	✓	✓
Intake of grain products	12	✓	✓	✓	✓
Intake of home produced foods	13	✓	✓	✓	✓
Total food intake	14	✓	✓	✓	✓
Human milk intake	15	✓		✓	
Total time indoors	16	✓			
Total time outdoors	16	✓			
Time showering	16	✓	✓	✓	✓
Time bathing	16	✓	✓	✓	✓
Time swimming	16	✓	✓	✓	✓
Time playing on sand/gravel	16	✓	✓	✓	✓
Time playing on grass	16	✓	✓	✓	✓
Time playing on dirt	16	✓	✓	✓	✓
Occupational mobility	16		✓		
Population mobility	16	✓	✓	✓	✓
Life expectancy	18	✓			
Volume of residence or building	19		✓	✓[b]	
Air exchange rates	19		✓	✓[b]	
✓ = Data available.					
[a] Including soil pica and geophagy.					
[b] Lower percentile.					

Table 1-2. Criteria Used to Rate Confidence in Recommended Values		
General Assessment Factors	Elements Increasing Confidence	Elements Decreasing Confidence
Soundness *Adequacy of Approach*	The studies used the best available methodology and capture the measurement of interest.	There are serious limitations with the approach used; study design does not accurately capture the measurement of interest.
	As the sample size relative to that of the target population increases, there is greater assurance that the results are reflective of the target population.	Sample size too small to represent the population of interest.
	The response rate is greater than 80% for in-person interviews and telephone surveys, or greater than 70% for mail surveys.	The response rate is less than 40%.
	The studies analyzed primary data.	The studies are based on secondary sources.
Minimal (or defined) Bias	The study design minimizes measurement errors.	Uncertainties with the data exist due to measurement error.
Applicability and Utility *Exposure Factor of Interest*	The studies focused on the exposure factor of interest.	The purpose of the studies was to characterize a related factor.
Representativeness	The studies focused on the U.S. population.	Studies are not representative of the U.S. population.
Currency	The studies represent current exposure conditions.	Studies may not be representative of current exposure conditions.
Data Collection Period	The data collection period is sufficient to estimate long-term behaviors.	Shorter data collection periods may not represent long-term exposures.
Clarity and Completeness *Accessibility*	The study data are publicly available.	Access to the primary data set was limited.
Reproducibility	The results can be reproduced, or methodology can be followed and evaluated.	The results cannot be reproduced, the methodology is hard to follow, and the author(s) cannot be located.
Quality Assurance	The studies applied and documented quality assurance/quality control measures.	Information on quality assurance/control was limited or absent.

Table 1-2. Criteria Used to Rate Confidence in Recommended Values (continued)		
General Assessment Factors	Increasing Confidence	Decreasing Confidence
Variability and Uncertainty *Variability in Population*	The studies characterize variability in the population studied.	The characterization of variability is limited.
Uncertainty	The uncertainties are minimal and can be identified. Potential bias in the studies are stated or can be determined from the study design.	Estimates are highly uncertain and cannot be characterized. The study design introduces biases in the results.
Evaluation and Review *Peer Review*	The studies received a high level of peer review (e.g., they are published in peer-reviewed journals).	The studies received limited peer review.
Number and Agreement of Studies	The number of studies is greater than three. The results of studies from different researchers are in agreement.	The number of studies is one. The results of studies from different researchers are in disagreement.

Table 1-3. Age-Dependent Potency Adjustment Factor by Age Group for Mutagenic Carcinogens		
Exposure Age Group[a]	Exposure Duration (year)	Age-Dependent Potency Adjustment Factor
Birth to <1 month	0.083	10×
1 <3 months	0.167	10×
3 <6 months	0.25	10×
6 <12 months	0.5	10×
1 to <2 years	1	10×
2 to <3 years	1	3×
3 to <6 years	3	3×
6 to <11 years	5	3×
11 to <16 years	5	3×
16 to <21 years	5	1×
≥21 years (21 to <70 years)	49	1×

[a]   U.S. EPA's recommended childhood age groups (excluding ages >21 years).
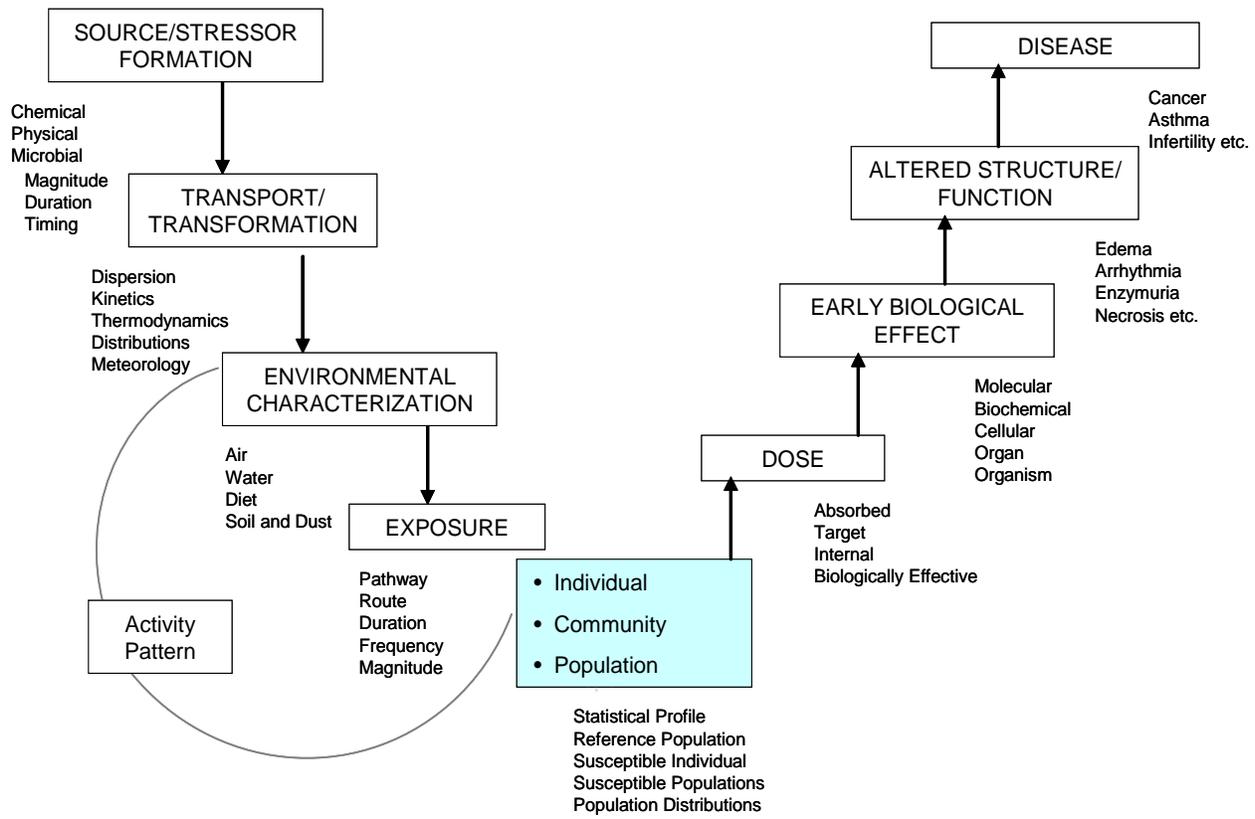
Figure 1-2. Exposure-Dose-Effect Continuum.

Source: Redrawn from U.S. EPA (2003c); WHO (2006); Ott (2007).

The exposure-dose-effect continuum depicts the trajectory of an agent from its source to an effect. The agent can be transformed and transported through the environment via air, water, soil, dust, and diet. Individuals can become in contact with the agent through inhalation, ingestion, or skin/eye contact. The individual's physiology, behavior, and activity patterns as well as the concentration of the agent will determine the magnitude, frequency, and duration of the exposure. The exposure becomes an absorbed dose once the agent crosses the absorption barrier (i.e., skin, lungs, eyes, gastrointestinal tract, placenta). Interactions of the chemical or its metabolites with a target tissue may lead to an adverse health outcome. The text under the boxes indicates the specific information that may be needed to characterize each step in the exposure-dose-effect continuum.
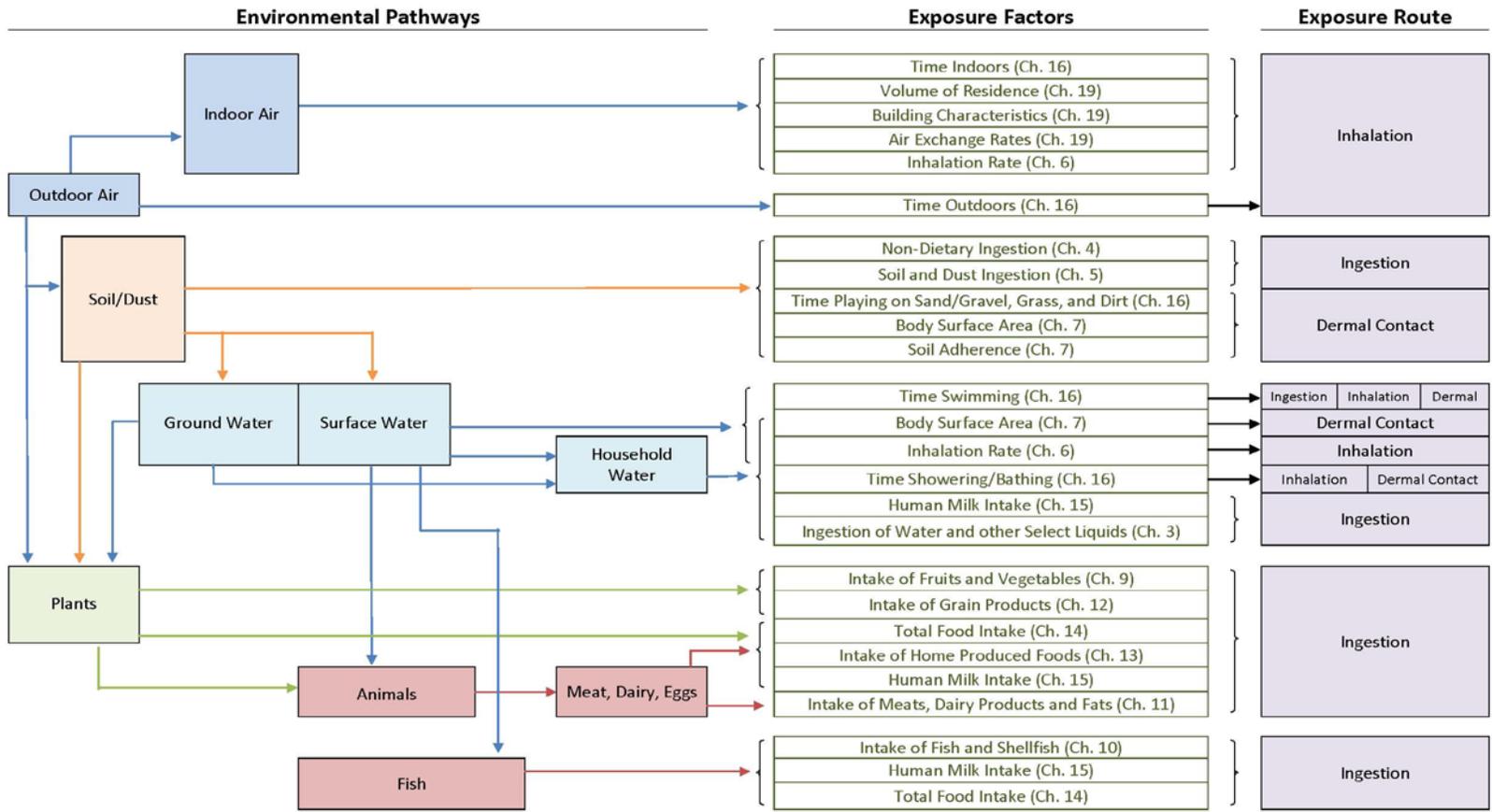
Figure 1-3. Schematic Diagram of Exposure Pathways, Factors, and Routes.

EXPOSURE ROUTE	EXPOSURE FACTOR	POPULATION	CHAPTER	RECOMMENDATIONS TABLE/RATINGS TABLE
Ingestion				
Inhalation				
Dermal				
(All Routes) Human Characteristics				
(All Routes) Activity Factors				
(All Routes) Consumer Product Use				
(All Routes) Building Characteristics				

Figure 1-4. Road map to Exposure Factor Recommendations.
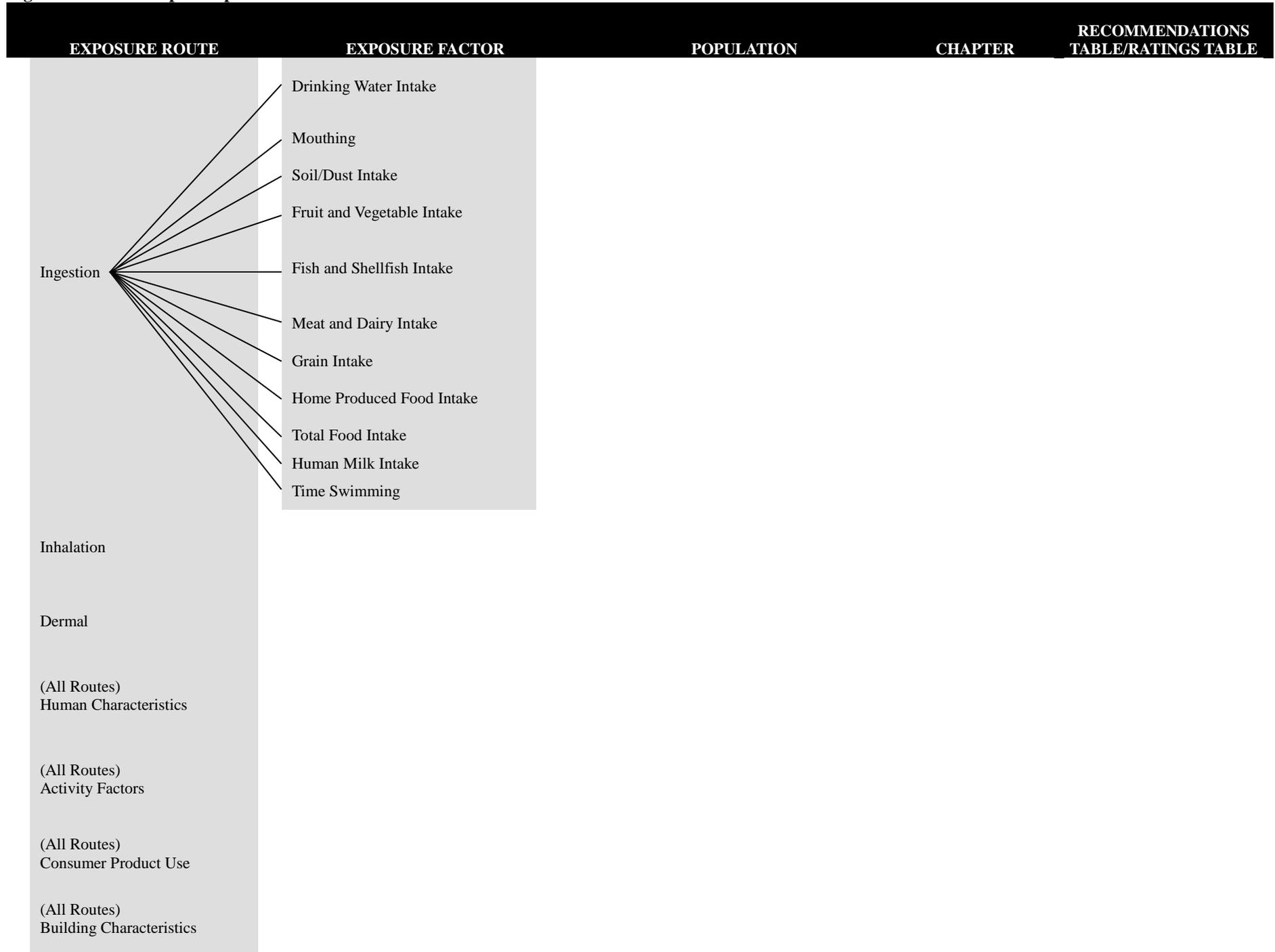
EXPOSURE ROUTE	EXPOSURE FACTOR	POPULATION	CHAPTER	RECOMMENDATIONS TABLE/RATINGS TABLE
Ingestion	Drinking Water Intake			
	Mouthing			
	Soil/Dust Intake			
	Fruit and Vegetable Intake			
	Fish and Shellfish Intake			
	Meat and Dairy Intake			
	Grain Intake			
	Home Produced Food Intake			
	Total Food Intake			
	Human Milk Intake			
	Time Swimming			
Inhalation				
Dermal				
(All Routes) Human Characteristics				
(All Routes) Activity Factors				
(All Routes) Consumer Product Use				
(All Routes) Building Characteristics				

EXPOSURE ROUTE	EXPOSURE FACTOR	POPULATION	CHAPTER	RECOMMENDATIONS TABLE/RATINGS TABLE
	Drinking Water Intake	Adults Children Pregnant Women	3	3-1 / 3-2 3-3 / 3-4
	Mouthing			
	Soil/Dust Intake			
	Fruit and Vegetable Intake			
	Fish and Shellfish Intake			
Ingestion	Meat and Dairy Intake			
	Grain Intake			
	Home Produced Food Intake			
	Total Food Intake			
	Human Milk Intake			
	Time Swimming			
Inhalation				
Dermal				
(All Routes) Human Characteristics				
(All Routes) Activity Factors				
(All Routes) Consumer Product Use				
(All Routes) Building Characteristics				

EXPOSURE ROUTE	EXPOSURE FACTOR	POPULATION	CHAPTER	RECOMMENDATIONS TABLE/RATINGS TABLE
Ingestion	Drinking Water Intake			
	Mouthing	Frequency Duration	4	4-1 / 4-2
	Soil/Dust Intake			
	Fruit and Vegetable Intake			
	Fish and Shellfish Intake			
	Meat and Dairy Intake			
	Grain Intake			
	Home Produced Food Intake			
	Total Food Intake			
	Human Milk Intake			
	Time Swimming			
Inhalation				
Dermal				
(All Routes) Human Characteristics				
(All Routes) Activity Factors				
(All Routes) Consumer Product Use				
(All Routes) Building Characteristics				

Commercial Buildings   19-3 / 19-4

EXPOSURE ROUTE	EXPOSURE FACTOR	POPULATION	CHAPTER	RECOMMENDATIONS TABLE/RATINGS TABLE
Ingestion	Drinking Water Intake			
	Mouthing			
	Soil/Dust Intake	Adults Children	5	5-1 / 5-2
	Fruit and Vegetable Intake			
	Fish and Shellfish Intake			
	Meat and Dairy Intake			
	Grain Intake			
	Home Produced Food Intake			
	Total Food Intake			
	Human Milk Intake			
	Time Swimming			
Inhalation				
Dermal				
(All Routes) Human Characteristics				
(All Routes) Activity Factors				
(All Routes) Consumer Product Use				
(All Routes) Building Characteristics				

EXPOSURE ROUTE	EXPOSURE FACTOR	POPULATION	CHAPTER	RECOMMENDATIONS TABLE/RATINGS TABLE
Ingestion	Drinking Water Intake			
	Mouthing			
	Soil/Dust Intake			
	Fruit and Vegetable Intake	Adults Children	9	9-1 / 9-2
	Fish and Shellfish Intake			
	Meat and Dairy Intake			
	Grain Intake			
	Home Produced Food Intake			
	Total Food Intake			
	Human Milk Intake			
	Time Swimming			
Inhalation				
Dermal				
(All Routes) Human Characteristics				
(All Routes) Activity Factors				
(All Routes) Consumer Product Use				
(All Routes) Building Characteristics				

EXPOSURE ROUTE	EXPOSURE FACTOR	POPULATION	CHAPTER	RECOMMENDATIONS TABLE/RATINGS TABLE
Ingestion	Drinking Water Intake			
	Mouthing			
	Soil/Dust Intake			
	Fruit and Vegetable Intake			
	Fish and Shellfish Intake	General Population Marine Recreational Freshwater Recreational Native American Populations	10	10-1 / 10-2 10-3 / 10-4 10-5 10-6
	Meat and Dairy Intake			
	Grain Intake			
	Home Produced Food Intake			
	Total Food Intake			
	Human Milk Intake			
	Time Swimming			
Inhalation				
Dermal				
(All Routes) Human Characteristics				
(All Routes) Activity Factors				
(All Routes) Consumer Product Use				
(All Routes) Building Characteristics				

EXPOSURE ROUTE	EXPOSURE FACTOR	POPULATION	CHAPTER	RECOMMENDATIONS TABLE/RATINGS TABLE
Ingestion	Drinking Water Intake			
	Mouthing			
	Soil/Dust Intake			
	Fruit and Vegetable Intake			
	Fish and Shellfish Intake			
	Meat and Dairy Intake	Adults Children	11	11-1 / 11-2
	Grain Intake			
	Home Produced Food Intake			
	Total Food Intake			
	Human Milk Intake			
	Time Swimming			
Inhalation				
Dermal				
(All Routes) Human Characteristics				
(All Routes) Activity Factors				
(All Routes) Consumer Product Use				
(All Routes) Building Characteristics				

EXPOSURE ROUTE	EXPOSURE FACTOR	POPULATION	CHAPTER	RECOMMENDATIONS TABLE/RATINGS TABLE
Ingestion	Drinking Water Intake			
	Mouthing			
	Soil/Dust Intake			
	Fruit and Vegetable Intake			
	Fish and Shellfish Intake			
	Meat and Dairy Intake			
	Grain Intake	Adults Children	12	12-1 / 12-2
	Home Produced Food Intake			
	Total Food Intake			
	Human Milk Intake			
	Time Swimming			
Inhalation				
Dermal				
(All Routes) Human Characteristics				
(All Routes) Activity Factors				
(All Routes) Consumer Product Use				
(All Routes) Building Characteristics				

EXPOSURE ROUTE	EXPOSURE FACTOR	POPULATION	CHAPTER	RECOMMENDATIONS TABLE/RATINGS TABLE
Ingestion	Drinking Water Intake			
	Mouthing			
	Soil/Dust Intake			
	Fruit and Vegetable Intake			
	Fish and Shellfish Intake			
	Meat and Dairy Intake			
	Grain Intake			
	Home Produced Food Intake	Adults Children	13	13-1 / 13-2
	Total Food Intake			
	Human Milk Intake			
	Time Swimming			
Inhalation				
Dermal				
(All Routes) Human Characteristics				
(All Routes) Activity Factors				
(All Routes) Consumer Product Use				
(All Routes) Building Characteristics				

EXPOSURE ROUTE	EXPOSURE FACTOR	POPULATION	CHAPTER	RECOMMENDATIONS TABLE/RATINGS TABLE
Ingestion	Drinking Water Intake			
	Mouthing			
	Soil/Dust Intake			
	Fruit and Vegetable Intake			
	Fish and Shellfish Intake			
	Meat and Dairy Intake			
	Grain Intake			
	Home Produced Food Intake			
	Total Food Intake	Adults Children	14	14-1 / 14-2
	Human Milk Intake			
	Time Swimming			
Inhalation				
Dermal				
(All Routes) Human Characteristics				
(All Routes) Activity Factors				
(All Routes) Consumer Product Use				
(All Routes) Building Characteristics				

EXPOSURE ROUTE	EXPOSURE FACTOR	POPULATION	CHAPTER	RECOMMENDATIONS TABLE/RATINGS TABLE
Ingestion	Drinking Water Intake			
	Mouthing			
	Soil/Dust Intake			
	Fruit and Vegetable Intake			
	Fish and Shellfish Intake			
	Meat and Dairy Intake			
	Grain Intake			
	Home Produced Food Intake			
	Total Food Intake			
	Human Milk Intake	Exclusively Breastfed Infants	15	15-1 / 15-2
	Time Swimming			
Inhalation				
Dermal				
(All Routes) Human Characteristics				
(All Routes) Activity Factors				
(All Routes) Consumer Product Use				
(All Routes) Building Characteristics				

EXPOSURE ROUTE	EXPOSURE FACTOR	POPULATION	CHAPTER	RECOMMENDATIONS TABLE/RATINGS TABLE
Ingestion	Drinking Water Intake			
	Mouthing			
	Soil/Dust Intake			
	Fruit and Vegetable Intake			
	Fish and Shellfish Intake			
	Meat and Dairy Intake			
	Grain Intake			
	Home Produced Food Intake			
	Total Food Intake			
	Human Milk Intake			
	Time Swimming	Adults Children	16	16-1 / 16-2
Inhalation				
Dermal				
(All Routes) Human Characteristics				
(All Routes) Activity Factors				
(All Routes) Consumer Product Use				
(All Routes) Building Characteristics				

| EXPOSURE ROUTE	EXPOSURE FACTOR	POPULATION		CHAPTER	RECOMMENDATIONS TABLE/RATINGS TABLE
Ingestion					
Inhalation	Inhalation Rate	Long Term	Adults Children	6	6-1 / 6-3
		Short Term	Adults Children		6-2 / 6-3
Dermal					
(All Routes) Human Characteristics					
(All Routes) Activity Factors					
(All Routes) Consumer Product Use					
(All Routes) Building Characteristics					

EXPOSURE ROUTE	EXPOSURE FACTOR	POPULATION	CHAPTER	RECOMMENDATIONS TABLE/RATINGS TABLE
Ingestion				
Inhalation				
Dermal	Body Surface Area	Adults Children	7	7-1, 7-2 / 7-3
	Adherence of Solids	Adults Children		7-4 / 7-5
(All Routes) Human Characteristics				
(All Routes) Activity Factors				
(All Routes) Consumer Product Use				
(All Routes) Building Characteristics				

EXPOSURE ROUTE	EXPOSURE FACTOR	POPULATION	CHAPTER	RECOMMENDATIONS TABLE/RATINGS TABLE
Ingestion				
Inhalation				
Dermal				
(All Routes) Human Characteristics	Body Weight Lifetime	Adults Children	8	8-1 / 8-2
(All Routes) Activity Factors				
(All Routes) Consumer Product Use				
(All Routes) Building Characteristics				

EXPOSURE ROUTE	EXPOSURE FACTOR	POPULATION	CHAPTER	RECOMMENDATIONS TABLE/RATINGS TABLE
Ingestion				
Inhalation				
Dermal				
(All Routes) Human Characteristics	Body Weight			
	Lifetime	Males Females	18	18-1 / 18-2
(All Routes) Activity Factors				
(All Routes) Consumer Product Use				
(All Routes) Building Characteristics				

EXPOSURE ROUTE	EXPOSURE FACTOR	POPULATION	CHAPTER	RECOMMENDATIONS TABLE/RATINGS TABLE
Ingestion				
Inhalation				
Dermal				
(All Routes) Human Characteristics				
(All Routes) Activity Factors	Activity Patterns	Adults Children	16	16-1 / 16-2
	Occupational Mobility	Adults		16-3 / 16-4
	Population Mobility	Adults Children		16-5 / 16-6
(All Routes) Consumer Product Use				
(All Routes) Building Characteristics				
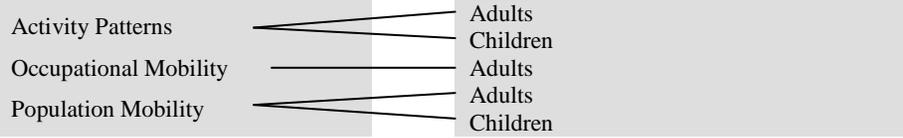
EXPOSURE ROUTE	EXPOSURE FACTOR	POPULATION	CHAPTER	RECOMMENDATIONS TABLE/RATINGS TABLE
Ingestion				
Inhalation				
Dermal				
(All Routes) Human Characteristics				
(All Routes) Activity Factors				
(All Routes) Consumer Product Use	Frequency of Use Amount Used Duration	General Population	17	No Recommendations
(All Routes) Building Characteristics				

EXPOSURE ROUTE	EXPOSURE FACTOR	POPULATION	CHAPTER	RECOMMENDATIONS TABLE/RATINGS TABLE
Ingestion				
Inhalation				
Dermal				
(All Routes) Human Characteristics				
(All Routes) Activity Factors				
(All Routes) Consumer Product Use				
(All Routes) Building Characteristics	Air Exchange Rates	Residential Buildings Commercial Buildings	19	19-1 / 19-2 19-3 / 19-4
	Building Volume	Residential Buildings Commercial Buildings		19-1 / 19-2 19-3 / 19-4

APPENDIX 1A

RISK CALCULATIONS USING EXPOSURE FACTORS HANDBOOK DATA AND DOSE-RESPONSE INFORMATION FROM THE INTEGRATED RISK INFORMATION SYSTEM (IRIS)

APPENDIX 1A—RISK CALCULATIONS USING EXPOSURE FACTORS HANDBOOK DATA AND DOSE-RESPONSE INFORMATION FROM THE INTEGRATED RISK INFORMATION SYSTEM (IRIS)

1A-1. INTRODUCTION

When estimating risk to a specific population from chemical exposure, whether it is the entire national population or some smaller population of interest, exposure data (either from this handbook or from other sources) must be combined with dose-response information. The dose-response information typically comes from the Integrated Risk Information System (IRIS) database, which maintains a list of toxicity (i.e., dose-response) values for a number of chemical agents (www.epa.gov/iris). Care must be taken to ensure that population parameters from the dose-response assessment are consistent with the population parameters used in the exposure analysis. This appendix discusses procedures for ensuring this consistency.

The U.S. EPA's approach to estimating risks associated with toxicity from non-cancer effects is fundamentally different from its approach to estimating risks associated with toxicity from carcinogenic effects. One difference is that different assumptions are made regarding the mode of action that is involved in the generation of these two types of effects. For non-cancer effects, the Agency assumes that these effects are produced through a non-linear (e.g., "threshold") mode of action (i.e., there exists a dose below which effects do not occur) (U.S. EPA, 1993). For carcinogenic effects, deemed to operate through a mutagenic mode of action or for which the mode of action is unknown, the Agency assumes there is the absence of a "threshold" (i.e., there exists no level of exposure that does not pose a small, but finite, probability of generating a carcinogenic response).

For carcinogens, quantitative estimates of risks for the oral route of exposure are generated using cancer slope factors. The cancer slope factor is an upper bound estimate of the increase in cancer risk per unit of dose and is typically expressed in units of $(mg/kg-day)^{-1}$. Because dose-response assessment typically involves extrapolating from laboratory animals to humans, a human equivalent dose (HED) is calculated from the animal data in order to derive a cancer slope factor that is appropriately expressed in human equivalents. The Agency endorses a hierarchy of approaches to derive human equivalent oral exposures from data in laboratory animal species, with the preferred approach being physiologically based toxicokinetic (PBTK) modeling. In the absence of PBTK modeling, U.S. EPA advocates using body weight to the ¾ power ($BW^{3/4}$) as the default scaling factor for extrapolating toxicologically equivalent doses of orally administered agents from animals to humans (U.S. EPA, 2011).

Application of the $BW^{3/4}$ scaling factor is based on adult animal and human body weights to adjust for dosimetric differences (predominantly toxicokinetic) between adult animals and humans (U.S. EPA, 2011). The internal dosimetry of other life stages (e.g., children, pregnant or lactating mothers) may be different from that of an adult (U.S. EPA, 2011). In some cases where data are available on effects in infants or children, adult PBTK models (if available) could be parameterized in order to predict the dose metric in children, as described in U.S. EPA's report, *A Framework for Assessing Health Risk of Environmental Exposures to Children* (U.S. EPA, 2011, 2006b). However, more research is needed to develop models for children's dosimetric adjustments across life stages and experimental animal species (U.S. EPA, 2006b).

In Summary:
- *No correction factors are applied to RfDs and RfCs when combined with exposure information from specific populations of interest.*
- *ADAFs are applied to oral slope factors, drinking water unit risks, and inhalation unit risks for chemicals with a mutagenic mode of action as in Table 1A-1.*
- *Correction factors are applied to water unit risks for both body weight and water intake rate for specific populations of interest.*

For cancer data from chronic animal studies, no explicit lifetime adjustment is necessary when extrapolating to humans because the assumption is that events occurring in a lifetime animal bioassay will occur with equal probability in a human lifetime. For cancer data from human studies (either occupational or general population), the Agency typically makes no explicit assumptions regarding body weight or human lifetime. For both of these parameters, there is an implicit assumption that the exposed population of interest has the same characteristics as the population analyzed by the Agency in deriving its dose-response information. In the rare situation where this assumption is known to be violated, the Agency has made appropriate

corrections so that the dose-response parameters are representative of the national average population.

For carcinogens acting through a mutagenic MOA, where chemical-specific data concerning early life susceptibility are lacking, early life susceptibility should be assumed, and the following ADAFs should be applied to the oral cancer slope factor, drinking water unit risks, and inhalation unit risks as described in the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005e) and summarized in Section 1.9 of this handbook:

- 10-fold for exposures occurring before 2 years of age;
- 3-fold for exposures occurring between the ages of 2 and 16 years of age; and
- no adjustment for exposures occurring after 16 years of age.

In addition to cancer slope factors, dose-response measures for carcinogens are also expressed as increased cancer risk per unit concentration for estimating risks from exposure to substances found in air or water (U.S. EPA, 1992b). For exposure via inhalation, this dose-response value is referred to as an IUR and is typically expressed in units of $(\mu g/m^3)^{-1}$. For exposure via drinking water, this dose-response value is termed the drinking water unit risk (U.S. EPA, 1992b). These unit risk estimates implicitly assume standard adult intake rates (i.e., 2 L/day of drinking water; 20-m^3/day inhalation rate). It is generally not appropriate to adjust the inhalation unit risk for different body weights or inhalation rates because the amount of chemical that reaches the target site is not a simple function of two parameters (U.S. EPA, 2009b). For drinking water unit risks, however, it would be appropriate for risk assessors to replace the standard intake rates with values representative of the exposed population of interest, as described in Section 1A-2 and Table 1A-1 below (U.S. EPA, 2005e).

As indicated above, for non-cancer effects, dose-response assessment is based on a threshold hypothesis, which holds that there is a dose above which effects (or their precursors) begin to occur. The U.S. EPA defines the RfD as "an estimate of a daily oral exposure for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime. It is derived from a benchmark dose lower confidence limit (BMDL), a no-observed-adverse-effect level, a

lowest-observed-adverse-effect level, or another suitable point of departure, with uncertainty/variability factors applied to reflect limitations of the data used." The point of departure on which the RfD is based can come directly from animal dosing experiments or occasionally from human studies followed by application of uncertainty factors to reflect uncertainties such as extrapolating from subchronic to chronic exposure, extrapolating from animals to humans, and deficiencies in the toxicity database. Consistent with the derivation of oral cancer slope factors noted above, the U.S. EPA prefers the use of PBTK modeling to derive HEDs to extrapolate from data in laboratory animal species, but in the absence of a PBTK model, endorses the use of $BW^{3/4}$ as the appropriate default scaling factor for use in calculating HEDs for use in derivation of the oral RfD (U.S. EPA, 2011). Body-weight scaling using children's body weight may not be appropriate in the derivation of the RfD because RfDs are already intended to be protective of the entire population including susceptible populations such as children and other life stages (U.S. EPA, 2011). Uncertainty factors are used to account for intraspecies variation in susceptibility (U.S. EPA, 2011). As indicated above, body-weight scaling is meant to predominantly address toxicokinetic differences between animals and humans and can be viewed as a dosimetric adjustment factor (DAF). Data on toxicodynamic processes needed to assess the appropriateness of body-weight scaling for early life stages are not currently available (U.S. EPA, 2011).

The procedure for deriving dose-response values for non-cancer effects resulting from the inhalation route of exposure (i.e., RfCs) differs from the procedure used for deriving dose-response values for non-cancer effects resulting from the oral route of exposure (i.e., RfDs). The difference lies primarily in the source of the DAFs that are employed. As with the RfD, the U.S. EPA prefers the application of PBTK modeling in order to extrapolate laboratory animal exposure concentrations to HECs for the derivation of an RfC. In the absence of a PBTK model, the U.S. EPA advocates the use of a default procedure for deriving HECs that involve application of DAFs. This procedure uses species-specific physiologic and anatomic factors relevant to the physical form of the pollutant (i.e., particulate or gas) and categorizes the pollutant with regard to whether it elicits a response either locally (i.e., within the respiratory tract) or remotely (i.e., extrarespiratory). These factors are combined in determining an appropriate DAF. The default dosimetric adjustments and physiological parameters used in RfC derivations assume an adult male with an air intake rate of 20

m^3/day and a body weight of 70 kg (U.S. EPA, 1994). Assumptions for extrathoracic, tracheobronchial, and pulmonary surface areas are also made based on an adult male (U.S. EPA, 1994). For gases, the parameters needed for deriving a DAF include species-to-species ratios of blood:gas partition coefficients. For particulates, the DAF is termed the regional deposition dose ratio and is derived from parameters that include region-specific surface areas, the ratio of animal-to-human minute volumes, and the ratio of animal-to-human regional fractional deposition. If DAFs are not available, simple ventilation rate adjustments can be made in generating HECs for use in derivation of the RfC (U.S. EPA, 2006b). Toxicity values (RfCs) derived using the default approach from the inhalation dosimetry methodology described in U.S. EPA (1994) are developed for the human population as a whole, including sensitive groups. Therefore, no quantitative adjustments of these toxicity values are needed to account for different ventilation rates or body weights of specific age groups (U.S. EPA, 2009b).

1A-2. CORRECTIONS FOR DOSE-RESPONSE PARAMETERS

The correction factors for the dose-response values tabulated in the IRIS database for non-cancer and carcinogenic effects are summarized in Table 1A-1. Use of these correction factors is necessary to avoid introducing errors into the risk analysis. This table is applicable in most cases that will be encountered, but it is not applicable when (a) the effective dose has been derived with a PBTK model, and (b) the dose-response data have been derived from human data. In the former case, the population parameters need to be incorporated into the model. In the latter case, the correction factor for the dose-response parameter must be evaluated on a case-by case basis by examining the specific data and assumptions employed in the derivation of the parameter.

It is important to note that the 2 L/day per capita water intake assumption is closer to a 90th percentile intake value than an average value. If an average measure of exposure in adults is of interest, the drinking water unit risk can be adjusted by multiplying it by 1.0/2 or 0.5, where 1.0 L/day is the average per capita water intake for adults ≥21 years old (see Chapter 3 of this handbook). If the population of interest is children, rather than adults, then a body-weight adjustment is also necessary. For example, the average water intake for children 3 to <6 years of age is 0.33 L/day (see Chapter 3 of this handbook), and the average body weight in this age

group is 18.6 kg (see Chapter 8 of this handbook). The water unit risk then needs to be adjusted by multiplying it by an adjustment factor derived from these age-group-specific values and calculated using the formula from Table 1A-1 as follows:

Water unit risk correction factor =

$$\left[\frac{0.33(L/day)}{2(L/day)}\right] \times \left[\frac{70(kg)}{18.6(kg)}\right] = 0.6 \quad \text{(Eqn. 1A-1)}$$

1A-3. REFERENCES FOR APPENDIX 1A

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Table 1A-1. Procedures for Modifying IRIS Risk Values for Non-Standard Populations	
IRIS Risk Measure [Units]	Correction Factor (CF) for Modifying IRIS Risk Measures[a]
RfD	No correction factor needed
RfC	No correction factor needed
Oral Slope Factor $[mg/(kg\text{-}day)]^{-1}$	No correction factor needed except for chemicals with mutagenic MOA. ADAFs are applied as follows: 10-fold for exposure occurring before 2 years of age 3-fold for exposure occurring between the ages of 2 and 16 - no adjustment for exposures occurring after 16 years of age
Drinking Water Unit Risk $[\mu g/L]^{-1}$	$[I_W^P/2] \times [70/(W^P)]$ For chemicals with mutagenic MOA, ADAFs are applied as follows: 10-fold for exposure occurring before 2 years of age 3-fold for exposure occurring between the ages of 2 and 16 - no adjustment for exposures occurring after 16 years of age
Inhalation Unit Risk $[\mu g/m^3]^{-1}$	No correction factor needed except for chemicals with mutagenic MOA. ADAFs are applied as follows: 10-fold for exposure occurring before 2 years of age 3-fold for exposure occurring between the ages of 2 and 16 - no adjustment for exposures occurring after 16 years of age

[a] Modified risk measure = (CF) × IRIS value.
W = Body weight (kg)
I_W = Drinking water intake (liters per day)
W^P, I_W^P = Denote non-standard parameters from the actual population of interest