A Framework for Assessing Health Risks of Environmental Exposures to Children

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LIST OF ABBREVIATIONS AND ACRONYMS

ADAF	Age-dependent adjustment factors
AUC	Area under the curve
BBDR	Biologically based dose-response
BMD	Benchmark dose
BMDL	Benchmark dose lower confidence level
CAA	Clean Air Act
CatReg	Categorical regression
C_{max}	Maximum concentration
CHAD	Consolidated Human Activity Database
CSF	Cancer slope factor
CYP	Cytochrome P450
DAF	Dosimetric adjustment factor
EPA	U. S. Environmental Protection Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act
GLP	Good laboratory practice
HEC	Human equivalent concentration
HED	Human equivalent dose
HEDS	Human Exposure Database System
LOAEL	Lowest-observed-adverse-effect level
MOA	Mode of action
MOE	Margin of exposure
NHEXAS	National Human Exposure Assessment Survey
NOAEL	No-observed-adverse-effect level
PBTK	Physiologically based toxicokinetic
POD	Point of departure
QRE	Quantitative risk estimation
RfC	Reference concentration
RfD	Reference dose
RfV	Reference value
SAR	Structure-activity relationship
TD	Toxicodynamic
TK	Toxicokinetic
TSCA	Toxic Substances Control Act
UF	Uncertainty factor
V_{max}	Maximum velocity
WOE	Weight-of-evidence

PREFACE

The mission of the U.S. Environmental Protection Agency (EPA) is to protect human health and the environment. In the early 1990s, the National Research Council (NRC) released a watershed report, *Pesticides in the Diets of Infants and Children,* regarding evaluation of risk to environmental exposures (NRC, 1993). Increased emphasis on protecting children from environmental exposures has evolved since this report due to mounting scientific evidence to support the vulnerability of the developing fetus and child. Legislative and administrative mandates have been enacted since this NRC report. In 1995, the EPA Administrator issued *Policy on Evaluating Health Risks to Children* (U.S. EPA, 1995a), which states that EPA will consider risks to infants and children consistently and explicitly as a part of risk assessments generated during its decision-making process, including the setting of standards to protect public health and the environment. Subsequent provisions in the Food Quality Protection Act (FQPA) (U.S. 104th Congress, 1996a) and the Safe Drinking Water Act (SDWA) Amendments (U.S. 104th Congress, 1996b) underscored this policy by focusing on the evaluation of children's exposures and toxicities in the context of risk assessment. Evaluation of environmental risks to children is an implicit consideration in human health risk assessment in other EPA legislative mandates (Clean Air Act [CAA] [U.S. 101st Congress, 1990]; Comprehensive Environmental Response, Compensation, and Liability Act [CERCLA] [U.S. 96th Congress, 1980], Toxic Substances Control Act [TSCA] [U.S. 94th Congress, 1976], Federal Insecticide, Fungicide, and Rodenticide Act [FIFRA] [U.S.104th Congress, 1996c]). In 1997, Presidential Executive Order 13045, *Protection of Children from Environmental Health Risks and Safety Risks* (Executive Order, 1997), gave further emphasis to the need for establishing potential risks from environmental exposures during childhood. The EPA subsequently published *Strategy for Research on Environmental Risks to Children* in 2000 (U.S. EPA, 2000f).

EPA risk assessment guidelines relevant to children's health issues have been published (U.S. EPA, 1991, 1996, 1998b, 2002a, 2005a,b,e), and other guidelines, policies, and recommendations are under development (U.S. EPA, 2002c). Implementation of the FQPA and the SDWA amendments required additional development of guidance and policy for protecting children's health. In response, the application of the FQPA 10-fold safety factor was discussed in the *Determination of the Appropriate FQPA Safety Factors(s) in Tolerance Assessment* (U.S. EPA, 2002d). Thus, there are a number of guidelines and policies related to children's health,

but no single, comprehensive document that can serve as a resource of information on children's health risk assessment.

In 1999, a draft report that collected information on current EPA guidance and practices was developed for the Office of Children's Health Protection (ICF Consulting, 1999). This report was a compendium of information on child-related risk assessment policy and methodology guidance at the time. This Framework document builds on that report and others referred to above by updating the information and linking to reference documents and other published information that can be used as a resource for those interested in children's health risk assessment.

Another major effort sponsored by EPA and others that serves as background for this document was a workshop held in Stowe, VT, July 30–August 2, 2001, organized by the International Life Sciences Institute (ILSI). The report of that workshop (ILSI, 2003) and subsequent publications (Daston et al., 2004; Ginsberg et al., 2004c; Landrigan et al., 2004; Morford et al., 2004; Olin and Sonawane, 2003) proposed a framework for children's exposures and health risk assessment and laid out a number of issues of concern. The Framework presented in this document builds on the efforts of the experts and participants at that workshop.

Parallel activities have been or are being developed at other agencies such as the U.S. Food and Drug Administration (FDA), which regulates pharmaceuticals, medical devices, biologics, food, animal feed and drugs, cosmetics, radiation-emitting devices, and combination products. For example, under the Best Pharmaceuticals for Children Act (U.S. FDA, 2002), an amendment to Section 11 of the Food and Drug Modernization Act (U.S. FDA, 1997), FDA's Office of Pediatric Therapeutics coordinates and facilitates all activities affecting the pediatric population, the practice of pediatrics, or pediatric issues within the FDA. Assessment of risks and benefits to children is conducted in compliance with the Pediatric Research Equity Act (U.S. 108th Congress, 2003), which requires that all applications for new active ingredients indications, dosage forms, dosing regimens, and routes of administration contain a pediatric assessment unless a waiver or deferral has been granted. Although the draft guidance document *Guidance for Industry - How to Comply with the Pediatric Research Equity Act* (U.S. FDA, 2005) may apply specifically to pharmaceutical testing and regulation, there can be significant overlap with assessments conducted to determine risk to children from environmental exposures. For example, *Guidance to Industry – Nonclinical Safety Evaluation of Pediatric Drug Products* (U.S.

FDA, 2006) addresses considerations on the evaluation of pharmaceuticals in juveniles, one of the lifestages discussed in this Framework.

Additionally, the International Programme for Chemical Safety of the World Health Organization recently developed a draft Environmental Health Criteria document entitled *Principles for Evaluating Health Risks Associated with Chemical Exposures to Children*. This EHC draft document serves as useful background information for using this EPA Framework.

Finally, EPA's Risk Assessment Forum has been working for several years to harmonize approaches to cancer and noncancer risk assessment (U.S. EPA, 1997c, 1998c). Efforts to develop a framework for a harmonized approach to human health risk assessment are underway, and the intent is for this Framework on health risks from environmental exposures to children to be incorporated into the overall framework.

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1. EXECUTIVE SUMMARY

The purpose of this document is to provide an overarching framework for a more complete assessment of children's exposure to environmental agents and the resulting potential health risks within the U.S. Environmental Protection Agency's (EPA's) risk assessment paradigm. This Framework examines the impact of potential exposures during developmental lifestages and subsequent lifestages, while emphasizing the iterative nature of the analysis phase with a multidisciplinary team. In addition to outlining the risk assessment process from a lifestage perspective, the document points to published sources for more detailed information. Guidance, policies, and other relevant materials are referenced in the document and linked electronically (when copyright allows) to the actual reference documents for easy access. In addition, many terms are included in a glossary at the end of this document. This Framework is a conceptual overview of the considerations for evaluation of early-life exposures and subsequent outcomes and does not constitute EPA guidance defined as a step-by-step process or standard operating procedure.

The term "children" as used in this document is shorthand to include the stages of development from conception through adolescence. EPA is concerned about health risks that result from exposure to all lifestages; however, this document focuses on preconceptional exposure and exposure throughout development to adulthood. *Developmental exposure* is used throughout this document to define developmental lifestage exposures (preconception through adolescence). Health risks may be identified during the same lifestage as when the exposure occurred, or they may not become apparent until much later in life.

Lifestages are defined in this document as temporal stages of life that have distinct anatomical, physiological, and behavioral or functional characteristics that contribute to potential differences in vulnerability to environmental exposures. A lifestage approach to risk assessment considers the relevant periods of exposure in developmental lifestages and subsequent outcomes that may not be expressed until later lifestages. This approach explicitly considers existing data as well as data gaps for both exposure and health outcomes at various lifestages.

Information on mode(s) of action (MOA) that may inform lifestages is another main emphasis of this approach. Risk assessment using a lifestage approach is a shift in perspective

from the current methodology that focuses primarily on adults, and then, secondarily, looks for information that may suggest greater susceptibility from exposures at other lifestages.

The added value of using a lifestage approach to risk assessment is a more comprehensive evaluation of the potential for vulnerability of the population at various lifestages. Children may be more or less vulnerable than adults, but without data on exposure and response and without systematic evaluation of these data, determining which lifestage may be more vulnerable is challenging. The approach outlined here encourages evaluation of the potential for toxicity and any adverse health outcomes during all developmental lifestages, based on knowledge of external exposure, critical windows of development for different organ systems, MOAs, anatomy, physiology, and behavior that can affect external exposure and internal dose metrics (units of measurement for dose). The use of MOA information is integral to this Framework and is employed in a consistent manner to the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (2005b). The MOA information is extended to the evaluation of all outcomes.

It is important to consider whether anything known about developmental lifestages would indicate particular vulnerability and incorporate that information into an assessment. This framework addresses the difficult issue of integrating toxicity data and exposure information, which is especially challenging when data are limited for particular lifestages (e.g., pregnancy and early childhood development).

The conceptual framework used in this document follows the basic components developed for other areas of risk assessment (U.S. EPA, 1997a, 1998a, 2003a) and includes problem formulation, analysis, and risk characterization as the three major phases in the process. Within this structure, questions for consideration in the process of scoping the problem to be addressed, reviewing the toxicity and exposure data, and characterizing the risks are posed as a way of prompting and refining the assessment process. Gaps in guidance needed for various aspects of assessing risk from children's exposure are also discussed. In particular, guidance is lacking for lifestage-specific evaluation of several system- and disease-specific areas, related biomarkers and outcomes, MOA(s), dose-response assessment, and exposure assessment. Also, guidance on the use of specific developmental or latent outcomes for application to risk assessments for various timing (exposure windows) and durations of exposure has not been

defined even though this issue is considered in many of the risk assessments currently being generated across EPA. Implementation of this Framework will necessitate development of guidance for children's health risk assessment.

2. INTRODUCTION AND PURPOSE

The purpose of this document is to provide an overarching framework for a more complete assessment of children's exposure to environmental agents and the resulting potential health risks. The term "children" as used in this document is shorthand to include the stages of development from conception through adolescence. EPA is concerned about health risks that result from exposure to all lifestages; however, this document focuses on exposures during preconception through adolescence. *Developmental exposure*, as used in this document, means developmental lifestage exposures (preconception through adolescence). Health risks may be identified during the same lifestage as when the exposure occurred, or they may not become apparent until much later in life.

The major encompassing question to be addressed by using this document is, What is the potential risk of environmental exposure during developmental lifestages? This Framework outlines the phases for assessing the risks of exposure to environmental agents during childhood, singly or in combination. This information can be used in various situations, depending on the problem to be addressed. For example, if an overall assessment of health risks is needed, the information on risks from developmental lifestage exposures can be incorporated into the overall assessment. If, on the other hand, the major concern is about health risks to children as a result of environmental exposure, the information derived from this process could be used directly to assess risk, set standards, and mitigate exposures.

In addition to outlining the process of assessing health risks as a result of environmental exposure during childhood, this framework uses existing sources for more detailed information which are referenced and linked to the actual reference documents (when copyright allows). These sources include guidelines, guidance documents, policies, and other relevant published materials that currently exist. This document incorporates this information while focusing on inherent and acquired susceptibility at different lifestages (e.g., children and adults), as well as the potential for greater exposure of environmental agents to children than adults.

The outline of this document follows the basic framework developed for other areas of risk assessment (U.S. EPA, 1997a, 1998a, 2003a) and includes problem formulation, analysis, and risk characterization as the three major phases in the process, each with a focus on lifestages (Figure 2-1, adapted from Daston et al., 2004; Olin and Sonawane, 2003). Each phase of the
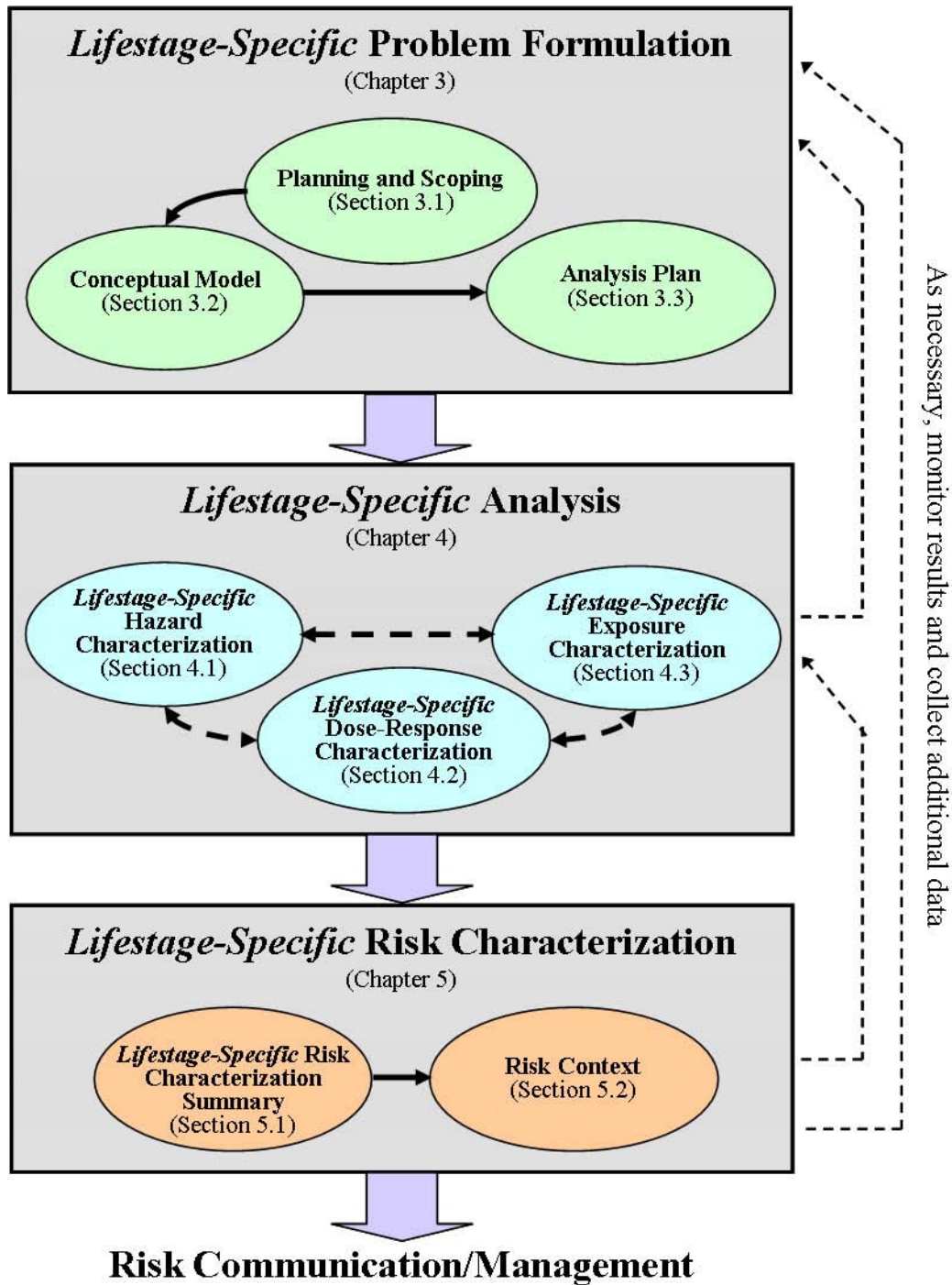
Figure 2-1. Flow diagram for a lifestage-specific risk assessment framework. This diagram presents the framework for lifestage-specific risk assessment used in this document. It is based on a number of documents on children's health risk assessment, including the ILSI workshop (Daston et al., 2004; Olin and Sonawane, 2003). It includes three phases also identified in *Guidelines for Ecological Risk Assessment* (U.S. EPA, 1998a) and *Framework for Cumulative Risk Assessment* (U.S. EPA, 2003a).

process raises questions to consider when assessing potential health risks to children from environmental exposure. Assessing potential health risks to children as a result of their environmental exposure to toxicants includes considering risk from exposure before conception, during the prenatal period, and through childhood and adolescence (Figure 2-2). Lifestages are defined in this document as periods of life with distinct anatomical, physiological, and behavioral or functional characteristics that contribute to potential differences in vulnerability to environmental exposures. *Preconception* is any time before conception; the *prenatal* stage includes the embryonic and fetal stages from conception to birth; *infancy* is the period from birth through the first birthday; *child* encompasses all early postnatal lifestages from birth until *adolescence*, which occurs approximately between 12 and 21 years of age (with difference between genders). The continuum between the reproductive-age adult and aged adult begins at approximately 21 years of age and reaches aged adulthood at approximately 65 years. Broad exposure interval categories (e.g., child) are shown in Figure 2-2 for illustration, and divisions between lifestages are not precise (e.g., there is some reproductive age overlap between the adolescent and the adult periods) (U.S. EPA, 2005c, 2002a, Table 3-1). The lifestages from conception through adolescence comprise the period of development; adverse outcomes may occur during that same lifestage or later in life. Neither the outcomes nor the risks from these developmental exposures will necessarily be the same for all lifestages. Rather, the outcomes will depend on the underlying developmental processes that determine susceptibility at the time of exposure. A lifestage approach for evaluating potential risks to children is a hypothesis-driven approach that takes into account all relevant periods of exposure explicitly considering where data do and do not exist for exposure and health outcomes. It focuses attention on considerations of early-life exposure and potential outcomes, which may be latent in their manifestation. This is predicated on considerations of MOA(s) for all lifestages of exposures. MOA is defined in this Framework as the sequence of key events and processes, starting with interaction of a toxic agent with a cell, proceeding through functional and anatomical changes, and resulting in the adverse health outcomes. "A key event is an empirically observable precursor step that is itself a necessary element of the MOA or is a biologically based marker for such an element" (U.S. EPA, 2005a,b). Both toxicokinetic (TK) and toxicodynamic (TD) steps are part of the mechanism and MOA leading to the toxic response (Andersen et al., 2000; Clewell et al., 2002a). As stated in the latest cancer guidelines, "MOA is contrasted with
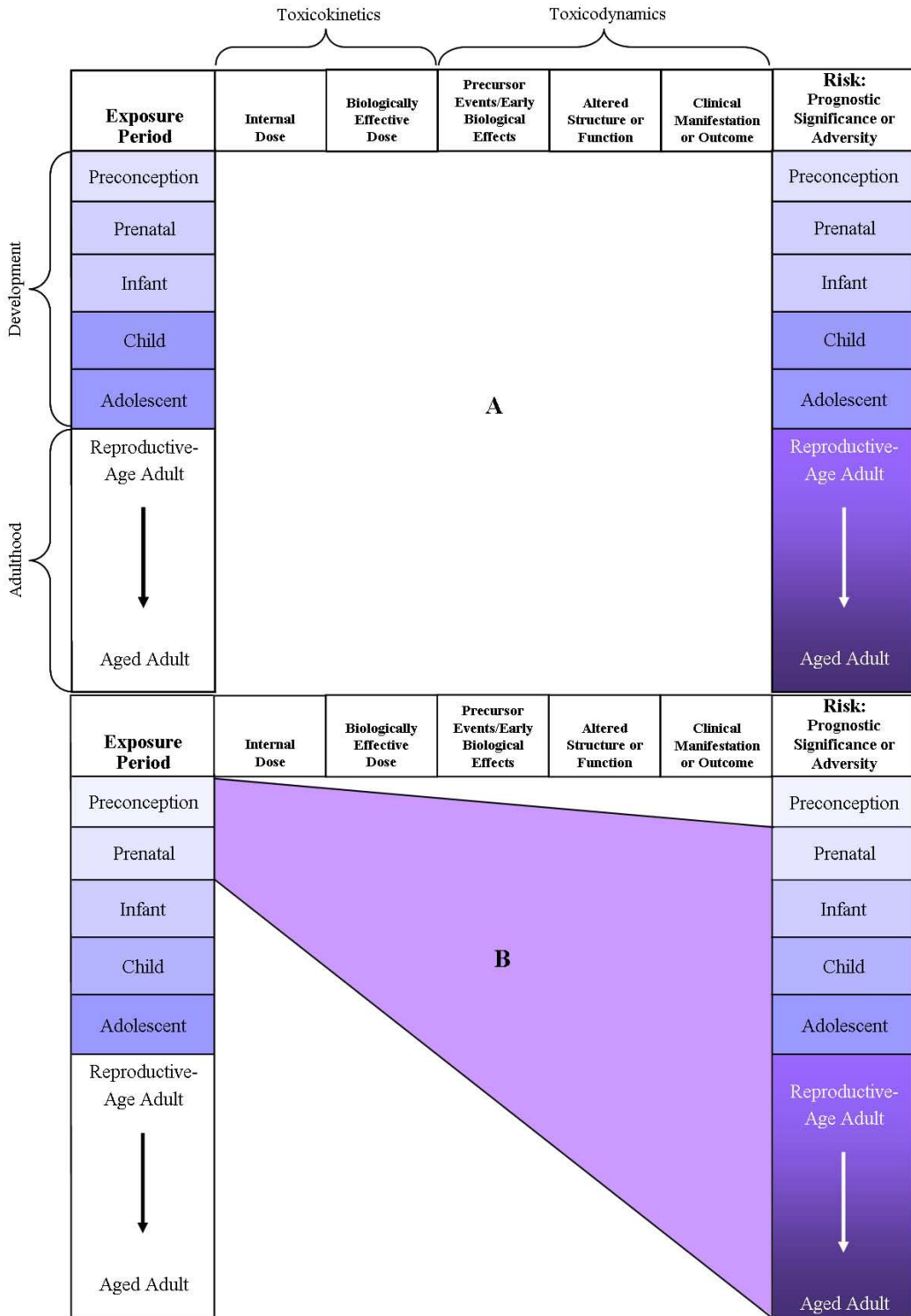
Figure 2-2. Lifestages of outcomes after developmental exposure. Panel A: In this figure, A illustrates the developmental lifestages of exposure considered in this document (shown in the shaded boxes on the left) and lifestages of potential outcomes considered in this document (shown in the shaded boxes on the right). The exposure to risk continuum is discussed across the top of the figure, and expanded upon in Figure 4-1. **Panel B:** Exposure during the preconception and prenatal stages may result in outcomes occurring in any lifestage beginning prenatally.

Exposure Period	Internal Dose	Biologically Effective Dose	Precursor Events/Early Biological Effects	Altered Structure or Function	Clinical Manifestation or Outcome	Risk: Prognostic Significance or Adversity
Preconception						Preconception
Prenatal						Prenatal
Infant			C			Infant
Child						Child
Adolescent						Adolescent
Reproductive-Age Adult ↓						Reproductive-Age Adult ↓
Aged Adult						Aged Adult

Exposure Period	Internal Dose	Biologically Effective Dose	Precursor Events/Early Biological Effects	Altered Structure or Function	Clinical Manifestation or Outcome	Risk: Prognostic Significance or Adversity
Preconception						Preconception
Prenatal						Prenatal
Infant						Infant
Child						Child
Adolescent			D			Adolescent
Reproductive-Age Adult ↓						Reproductive-Age Adult ↓
Aged Adult						Aged Adult

Panel C: Exposure during infancy and childhood may result in outcomes occurring in any lifestage beginning in infancy. **Panel D:** Exposure during the adolescent stage may result in outcomes occurring in any lifestage beginning in adolescence.

mechanism of action, which implies a more detailed understanding and description of events, often at the molecular level" (U.S. EPA, 2005a,b). Risk assessments may require a more refined definition of exposure intervals (e.g., bins) than the lifestages shown in Figure 2-2 because of rapid changes during development, even within a lifestage. For example, gestational exposure is typically evaluated for each trimester; however, specific periods of vulnerability (also known as critical windows) for particular outcomes might be much shorter period of time as discussed in a series of publications that resulted from an EPA-sponsored workshop (Selevan et al., 2000).

    This report synthesizes the information currently available at EPA on assessing health risks as a result of children's exposures and is based in part on existing risk assessment guidelines, guidance, and science policies. Also, areas and topics are identified where further guidance and research is needed. Within this structure, questions to be considered in the process of reviewing data are posed as a way of prompting the data evaluation. This Framework is not a guideline or science policy paper but rather describes an overall vision of the structure, process, and the components considered important for assessing risks as a result of children's exposure. This document intends to provide documentation of the approaches for assessing risk to children. It is not intended to be prescriptive or to define a step-by-step process or standard operating procedure.

    The primary intended users of this approach are risk assessors involved in hazard, dose-response, and exposure characterization. The central focus of this Framework is the prenatal stage, infancy, childhood, and adolescence, thus extending and expanding the approach in *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991), which only focuses on prenatal outcomes. The Framework also takes a child-protective approach to assessing risk (Landrigan et al., 2004) by putting the child, rather than an environmental agent, at the focus of the evaluation. Children are not a unique population but rather childhood is a series of lifestages through which all individuals pass; therefore, a child-protective approach is inherently public health-oriented.

    The added value of using a lifestage approach to assess risks to children from environmental exposure is a comprehensive evaluation of the potential for vulnerability of various lifestages. In contrast, assessments that use only available chemical-specific data, which are often limited to data from adults, do not necessarily account for the lack of data at other lifestages. The approach outlined here encourages evaluation of the potential for toxicity during

all developmental lifestages, based on what is known about critical windows of development for different organ systems and differences in anatomy, physiology, and behavior that can impact external exposure and internal dose metrics. In developing an assessment, the lack of data for certain lifestages is not meant to imply susceptibility and/or greater uncertainty in the assessment of risk from childhood exposure. Rather, the intent is to consider whether anything is known about lifestages that would indicate particular vulnerability during that stage and incorporate that information into the assessment. This document also addresses the difficult issue of integrating animal toxicity or adverse health outcome data and exposure information relevant for assessing risks to humans. This integration is especially challenging because of data limitations for particular periods during pregnancy and early childhood development. One result of using this framework will be more transparent and scientifically justifiable risk characterizations, while documenting data gaps and identifying priority data needs for children's risk.

The approach outlined here encourages evaluation of the potential for toxicity during all developmental lifestages, based on what is known about critical windows of development for different organ systems, MOAs, anatomy, physiology, and behavior that can affect external exposure and internal dose metrics.

Because of the complex issues to be considered for assessing risks from children's exposures, it is impossible for any one person to be an expert in all areas of this process. Thus, consultation and collaboration with appropriate experts in hazard, dose-response, and exposure assessment is recommended in all phases of the process.

3. LIFESTAGE-SPECIFIC PROBLEM FORMULATION

Problem formulation is a systematic planning phase that defines the problem to be addressed in the assessment. The purpose of a problem formulation phase is to aid in efficiency and transparency of the assessment. A general discussion of problem formulation can be found in the *Framework for Cumulative Risk Assessment* (U.S. EPA, 2003a). The major components of problem formulation are no different whether applied to broad assessment (e.g., National Ambient Air Quality Standards, U.S. EPA, 2005d) of all lifestages of exposure or to a narrow assessment of specific lifestages of exposure (e.g., Superfund site). However, some of the specific considerations are different in a risk assessment for developmental exposures.

The lifestage-specific problem formulation phase establishes the context of the risk assessment and feeds into the lifestage-specific analysis phase (Chapter 4) and ultimately to lifestage-specific risk characterization (Chapter 5). A planning and scoping step (Section 3.1) initially characterizes exposures and outcomes during all developmental lifestages. The problem formulation results in two products. First, a conceptual model (Section 3.2) is developed which considers exposures (e.g., sources, receptors, stressors, pathways, individual characteristics) and outcomes. Second, an analysis plan (Section 3.3) is developed, where preliminary consideration of study methods, dose-response models, data gaps, and uncertainty and variability is used to inform hazard characterization, dose-response characterization, and exposure characterization (Figure 3-1).

These products are then used in the lifestage-specific analysis (Chapter 4), which comprises hazard characterization (Section 4.1), dose-response characterization (Section 4.2), and exposure characterization (Section 4.3). Iteration between each of the three analysis steps may lead to further refinement of the conceptual model and analysis plan.

3.1. PLANNING AND SCOPING

In the planning and scoping step, the assessment goals, breadth, and focus are established, and regulatory and policy factors are identified. This step includes defining and identifying the purpose, scope, participants/stakeholders, approaches, resources, and relevant past assessments available.
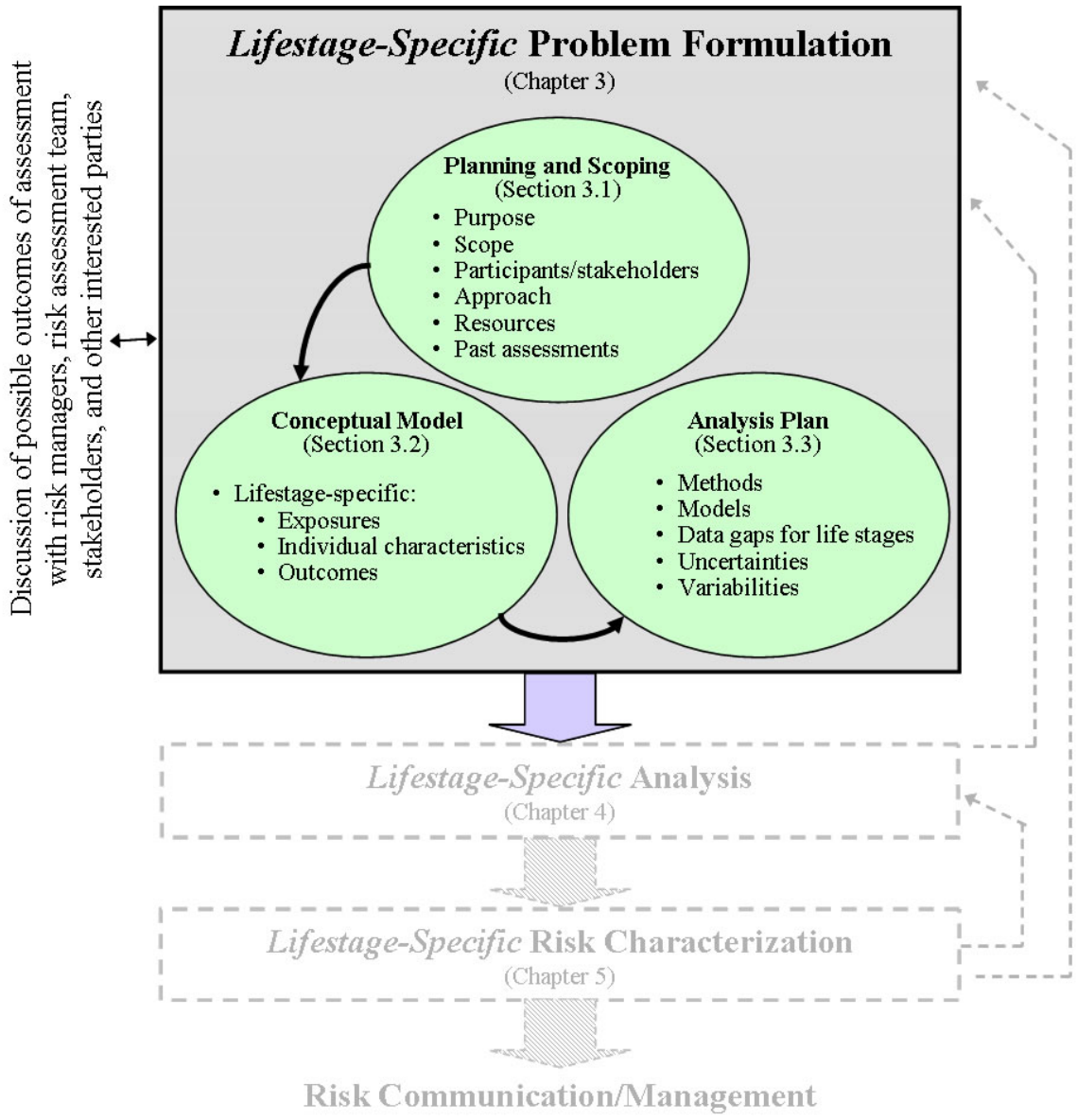
Figure 3-1. Flow diagram for lifestage-specific problem formulation. Problem formulation includes a planning and scoping step that initially characterizes exposures and outcomes during all developmental lifestages, and the development of two products: a conceptual model and an analysis plan.

Source: Adapted from U.S. EPA, 2003a, Figure 1-3.

A clear purpose of the assessment is defined in order to guide the lifestage-specific risk assessment strategy. Risk assessments are often conducted within the context of a regulatory requirement (e.g., CAA, U.S. 101st Congress, 1990; FQPA, U.S. 104th Congress, 1996a; SDWA, b), a community need, a health concern, or some other driving force (U.S. EPA, 2003a), and they require varying levels of scope or depth (U.S. EPA, 2005a, Section 1.2.2). For example, there may be judicial and societal considerations that may influence the timing and breadth of the assessment (e.g., consent agreement on soil contamination for a site-specific cleanup). These factors may influence the risk management options, management goals, key participants, data sources, selection of assessment outcomes, or the schedule for developing the assessment. The risk management and assessment planning teams need to develop dialogue on the regulatory basis for the risk assessment and determine what kind of information is needed to satisfy such requirements.

The scope sets the parameters of the assessment, allowing for decisions to include or exclude various elements. Screening level analyses of hazard and exposure may help refine the scope of the assessment. The scope can be narrow (e.g., at a site where soil screening levels are developed with lifestage-specific data) or broad (e.g., national rule-making, tolerance setting), depending upon the problem. Age-specific information on factors related to exposure and response are considered in the analysis plan (Section 3.3).

Choosing the appropriate participants for problem formulation will depend on the problem being addressed. The participants who have information, expertise, or a stake in the assessment process and conclusion(s) of the assessment are identified in this planning and scoping step. Stakeholders are broadly defined as the interested parties who are concerned with the decisions made about how a risk may be avoided, mitigated, or eliminated, and as those who may be affected by regulatory decisions. This process can include specialized expertise and a basic understanding of critical windows of exposure and optimum timing for evaluating outcomes. The risk assessment team (which may include epidemiologists, toxicologists, public health specialists, child behavior specialists, exposure assessors, chemists, and other technical experts) and the risk management team (which may include economists, policy analysts, engineers, and public health specialists) work together, informed by stakeholder input (which may include parents, pediatricians, community groups, non-governmental organizations, etc.) to develop the rationale, scope, and relevant outputs for the risk assessment and characterization

(U.S. EPA, 2001a). The conceptual model and analysis plan, including the possible outputs of the assessment, may require negotiation among the members of the risk assessment team. The *Framework for Cumulative Risk Assessment* (U.S. EPA, 2003a, p. 21) provides guidelines for stakeholder involvement, which are based on the recommendations in *Science and Judgment in Risk Assessment* (NRC, 1994) and by the Presidential/Congressional Commission on Risk Assessment and Risk Management (1997a,b).

Methods used for risk assessment of health outcomes can have an impact on the economic evaluation in benefits analysis (Griffiths et al., 2002; U.S. EPA, 2000a, 2003b, 2005e) (Section 5.1.7). Bringing economists into the discussion at the problem formulation stage will help clarify the approaches needed for data evaluation and quantification that may be most useful for assessing benefits. Another key consideration here is the selection of outcomes for which economic valuation will be considered in the assessment, because this includes dialogue between risk assessors and economists.

Identifying available resources to achieve assessment goals within the time frame of the assessment involves a qualitative screening evaluation of resources, which may or may not identify whether children have a greater potential for higher exposures or greater intrinsic susceptibility. The evaluation includes a preliminary examination of the quality and quantity of the available data on exposure and outcomes. More detailed evaluations (refined assessment) may or may not be necessary or may not be possible, depending on the available data. Where adequate data exist (particularly on potential critical windows of exposure, level of exposure, individual and community characteristics, optimum timing of outcome evaluation, and the magnitude of concerns about the public health outcome), a more detailed approach can be employed to address important questions for the exposure and health effects characterization. These include identifying past assessments that relate to the purpose and scope of the assessment and that may assist the process with existing tools, methods, or models.

- Why is the risk assessment being done? What are the needs of the assessment? Is there a regulatory driver(s)?

- What is the public health concern? Is there a specific concern for developmental lifestage exposure?

- What is the risk question(s) being asked, and is it lifestage-specific? Will the assessment consider exposure at all lifestages or exposure at specific developmental lifestages?

- Which lifestage(s) (age bin[s]) is likely to have the greatest external exposure, the greatest internal dose, and the greatest inherent vulnerability?

- Have other risk assessments included consideration of health risks from children's exposures on this chemical (e.g., EPA, other federal agencies, other organizations)?

3.2. CONCEPTUAL MODEL

Within the conceptual model, the risk assessment team develops preliminary hypotheses about why adverse effects have occurred or may occur in the future. A conceptual model is developed, keeping in mind the relationships among the individual characteristics, exposures, and outcomes. The relationships are informed by the initial identification of lifestage-specific exposure scenarios, the lifestage of exposure, the optimum times for evaluation of outcomes that will be addressed and the identified characteristics and toxicologic outcomes of the chemical(s) that may contribute to latent effects from early exposure and children's risk.

A qualitative characterization of hazard and exposure for specific lifestages results in the accumulation of the information needed to develop a conceptual model that aids the segue from the problem formulation stage to the analysis phase. The conceptual model is the starting point for the lifestage-specific analysis phase (Chapter 4) and can be presented as a diagram, a flow chart, or a narrative description of the predicted key relationships (U.S. EPA, 2002b).

The following provides an approach to a preliminary evaluation of the available exposure data (Section 3.2.1), outcome data (Section 3.2.2), and the integration of the two (Section 3.2.3) to help define the conceptual model and aid in the development of a problem-driven analysis plan with a focus on lifestages.

3.2.1. Exposure Considerations

The exposure considerations include performing a preliminary examination of the data to determine the lifestages likely to be exposed, given the chemical properties and uses of the environmental agent(s) in the defined scope of the assessment. The preliminary examination involves a qualitative characterization of the sources, pathways of exposures (including exposure

media and routes), exposure scenarios (lifestages, time frames, locations, and activities), and pattern of exposures (magnitude and duration) to parents or children, as appropriate, including the potential for dietary, drinking water, soil and air exposures, and other exposure media (e.g., pharmaceuticals) (U.S. EPA, 1992, 2002c).

An issue to consider is whether all lifestages are at the same risk from a given exposure or whether a specific developmental lifestage is more vulnerable because of higher exposures or intrinsic susceptibility. This includes a qualitative understanding of lifestage-specific activity patterns to identify potentially highly exposed lifestages. Currently, EPA's *Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants* (U.S. EPA, 2005e) is to be used as a starting point for identifying and selecting age bins for analysis (see Table 3-1). This guidance includes expert analysis of existing generic exposure data. This guidance provides a detailed discussion of how these age groups were developed and how to implement them in an assessment. In brief, the recommended age groups are based on the current understanding of differences in behavior and physiology that may impact exposures to children. Information on critical windows of susceptibility also is factored into these age bin considerations for potential vulnerability at different lifestages.

Typically, the conceptual model will consider human exposure in the context of the source-to-effects paradigm (U.S. EPA, 2003b, Figure 1-3). When formulating an exposure assessment, it is useful to qualitatively evaluate this model from the "effects" back to the "source." In this way, potentially important time periods of exposure, exposure pathways, and vulnerable individuals or populations can be identified. However, as the risk assessment becomes more complex, some limitations in the source-to-effect model become apparent. Exposure assessments using a source-to-effect model are based on the characteristics of the specific source of the exposure (e.g., geographical location, release rate, point source) and not the characteristics of the lifestage being exposed. As a result, only individuals or populations with exposure to this specific source are included in the model. Yet, exposure may result from multiple independent sources, all of which could contribute toward total exposure to a chemical or mixture of chemicals. In this case, a person-oriented exposure assessment better characterizes the person and lifestage of interest along with the applicable sources than a population-oriented exposure assessment.

Table 3-1. Developmental lifestages and age groups for exposure assessments.

Lifestages	Age Groups[a]
Preconception	reproductive age adult
Prenatal	conception to birth
Infant	birth to <1 month
	1 to <3 months
	3 to <6 months
	6 to <12 months
Child	1 to <2 years
	2 to <3 years
	3 to <6 years
Adolescent	6 to <11 years
	11 to <16 years
	16 to <18 years
	18 to <21 years

[a] The age groupings from birth to adulthood are from U.S. EPA (2005e). These standard age groups were developed based on the results of a peer involvement workshop (U.S. EPA, 2000b) focused on developmental changes in behavior and physiology impacting exposures to children.

Below are some questions that are useful in framing the examination of exposure considerations.

- What data are available that characterize children's exposure?

- Will the risk assessment consider all possible sources, media, pathways, and routes of exposure (aggregate and cumulative), or is it confined to specific scenarios (e.g., children living near a specific Superfund site and potentially exposed via air, soil, and groundwater)?

- Is it suspected that individuals in developmental lifestages are actually being exposed to the compound?

- What are the potential exposure sources, media (e.g., breast milk, indoor air), pathways, and routes of exposure?

- What are the human lifestage behaviors (e.g., mouthing, crawling), activities (e.g., bathing, sleeping), and locations (e.g., indoors, outdoors, daycare) that may impact exposure?

- What other individual or community characteristics may be present that could put children at higher risk of exposure and thus make them more vulnerable (e.g., pre-existing diseases or disorders, belonging to a farm worker family, socio-economic status, poor nutrition, sanitation conditions, cultural practices)?

- What are elements of the physical environment that may impact exposure (e.g., altitude, climate, urban vs. rural)?

3.2.2. Outcome Considerations

In this screening approach, a preliminary identification of toxic effects is performed, including TK and TD profiles, including to what degree these data support a hypothesized MOA(s). Evaluating critical windows of susceptibility and number of critical effects that have been observed relevant to the problem or scenario of concern for the risk assessment can be used to qualitatively assess the database. This qualitative assessment assures that the risk assessment team is appropriately staffed and has the essential resources to meet the timetables established in the analysis plan.

Below are some questions that are useful in framing the examination of hazard and dose-response considerations.

- What toxicology, epidemiology, or other data are available that examine outcomes following exposure to the chemical(s) of interest?

- Are there any suspected MOAs and other factors to be considered for relevant child health outcomes?

- Are there TK (e.g., metabolic activation/conjugation) or TD (e.g., MOA) considerations during certain developmental lifestages that may make the chemical more or less toxic?

- What do we know about the properties of the chemical being evaluated that may be important for considering lifestage-specific risk?

- Does the chemical cause known organ-specific toxicity? How might these organs be differentially susceptible during development?

- What is known about critical windows of exposure (e.g., developmental windows of susceptibility) for humans? For the experimental animal species and strain?

- What is known about critical windows of effect (e.g., latent expression of developmental toxicity) for the experimental animal species and strain?

- Are there any toxicologic outcomes noted in animal or human studies that are signals of possible increased susceptibility of developmental lifestages (e.g., carcinogenicity, neurotoxicity, immunotoxicity, endocrine disruption)?

- What are the background rates for outcomes of concern in the general population?

- What dose metrics (AUC or C_{max}) are being considered for the lifestage-specific assessment?

3.2.3. Integrating Exposure and Outcome Considerations

The concepts of timing and dosimetry are incorporated as unifying factors for both exposure and hazard components of the analysis. In a child-centered approach, multiple stressors may need to be considered for a particular outcome of interest due to convergence on a common MOA, as well as possible confounding, effect modification, or bias present in some studies. Additional stressors may have an impact on behavior. For example, a person with asthma may be less active or spend less time outside where an exposure may occur. Dialogue between experts such as exposure scientists, health scientists, epidemiologists, and toxicologists will ensure that the critical windows of exposure and critical effects are sufficiently identified, at least at a qualitative level, for the development of a conceptual model and an adequate analysis plan (Section 3.3). Below are some questions that are useful when integrating exposure and response considerations.

- How do chemical sources, fate, and transport influence target outcomes for various lifestages?

- How do magnitude, patterns, and pathways of exposure influence target outcomes for various lifestages?

- How does lifestage-specific dosimetry impact the temporal resolution required for exposure assessment?

- Based on the transport and fate of the chemical under evaluation, do the available exposure and hazard data address the compound(s) to which children may actually be exposed?

- Can exposure to multiple stressors during a critical window of development lead to modification of a health outcome of interest (e.g., additivity, synergism, antagonism)?

3.3. ANALYSIS PLAN

The analysis plan identifies the methods, models, critical data gaps, major variabilities and uncertainties, and key assumptions to be considered as the problem-driven assessment moves forward to a more in-depth lifestage-specific analysis (Chapter 4). The analysis plan is a working outline that provides the rationale for the resources (expertise, time, and finances) required to complete the assessment. Examination of the most vulnerable age groups and key risk drivers relevant to the problem identified will help conscribe the assessment and shape the decision points and decision tree in the analysis plan.

A database inventory may be useful for identifying data gaps (Table 3-2). This table presents an example of a database inventory method. After assessing the available information on lifestages of exposure, the assessor can note whether there are the various types of information for each lifestage. For example, are there human studies assessing outcomes after *in utero* exposure? In many instances, few of these fields will have data. Input from the relevant risk managers may be needed on the scope of the conceptual model and analysis plan, particularly with respect to the questions the assessment is meant to answer. This exercise can facilitate identification of strengths and weaknesses in the database, especially with regard to a lifestage-specific assessment. Many of these boxes will be blank for most chemicals; these data gaps do not necessarily represent research needs, but the data gaps may be useful in identifying where more information would be helpful and communicate this need to conduct research. For example, if the problem formulation suggests that infants have a potentially high risk due to biological susceptibility or probability of increased exposure, then absence of data for that lifestage may affect the relevancy of the risk assessment to address the identified problem or question of the assessment.

Planning and scoping (Section 3.1), the conceptual model (Section 3.2), and the analysis plan (Section 3.3) are then used in the lifestage-specific analysis (Chapter 4), which comprises hazard characterization (Section 4.1), dose-response characterization (Section 4.2), and exposure characterization (Section 4.3). Further scoping may be considered in each of the three analysis steps, thus leading to further refinement of the conceptual model and analysis plan.

Table 3-2. Lifestage-specific database inventory sheet. Types of information are described in the left-hand column, and lifestages of exposure are shown in the top row.

		Preconception	In Utero	Infant	Child	Adolescent	Adult
Lifestage-Specific Hazard Characterization	Human studies						
	Animal studies						
Lifestage-Specific Dose-Response Characterization	Toxicokinetic data						
	Toxicodynamic data						
	Mode of Action						
Lifestage-Specific Exposure Characterization	Chemical properties, environmental sources, fate and transport						
	Environmental media concentrations						
	Lifestage-specific exposure measurement data						
	Lifestage-specific exposure factors						

Developmental lifestages span In Utero through Adult.

- Does the analysis plan focus on what are likely to be the most vulnerable age groups?

- Does the analysis plan focus on the key risk drivers?

- What decision points are needed in the analysis plan for the specific problem identified?

4. LIFESTAGE-SPECIFIC ANALYSIS

The analysis phase of risk assessment includes hazard characterization (Section 4.1), dose-response characterization (Section 4.2), and exposure characterization (Section 4.3), where data are analyzed, both qualitatively and quantitatively. Iterations among all three steps provide communication among the risk assessment team members and refine the focus on the key assessment questions identified in the problem formulation phase (Chapter 3). These iterations are performed to enhance, but not effectively delay, the final assessment.

Focusing on data with outcomes after exposure during developmental lifestages of greatest susceptibility (i.e., critical windows) is key to the lifestage-specific evaluation of hazard, dose-response, and exposure data. These data may identify critical windows of exposure and data gaps for particular lifestages of exposure. MOA information based on TK and TD data may inform the lifestage-specific analysis (Figure 4-1).
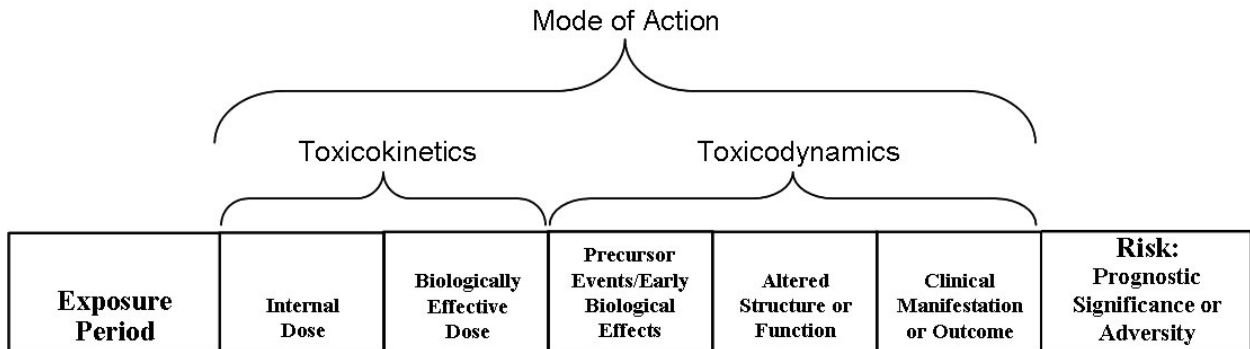
Figure 4-1. Exposure to risk continuum. This figure identifies the major elements in Figure 2-2a. This includes specific elements of TK and TD that may be lifestage-specific. This TK and TD information (MOA) can lead to increased characterization of the altered structural and functional outcomes

Source: Adapted from: Schulte, 1989.

The next three Sections (4.1, 4.2, and 4.3) discuss the three steps of the analysis phase and provide information to guide the assessor through the process (Figure 4-2). In order to link exposures and outcomes appropriately, an iterative process among all steps of the analysis is suggested for a robust risk characterization, the final phase in the risk assessment process (Chapter 5).
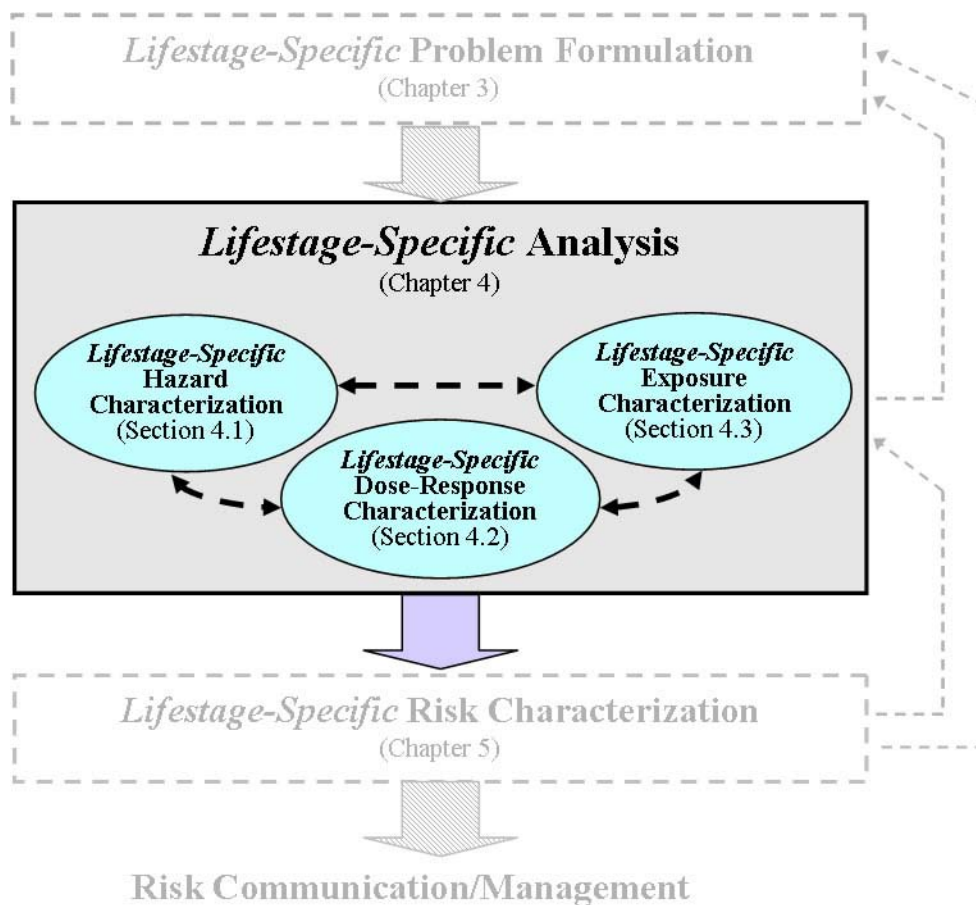
Figure 4-2. Flow diagram for lifestage-specific analysis. Following the problem formulation stage, the three steps of the analysis phase include hazard characterization (Section 4.1), dose-response characterization (Section 4.2), and exposure characterization (Section 4.3). This is followed by the risk characterization (Chapter 5) and risk communications/management phases.

4.1. LIFESTAGE-SPECIFIC HAZARD CHARACTERIZATION

4.1.1. Introduction

Hazard characterization is the analysis step in which the data are evaluated for potential adverse health effects. Hazard characterization begins with the identification of the human and animal toxicology studies to be included in the database. It includes the identification of any outcomes associated with exposure at specific doses. The primary purpose of a lifestage-specific hazard characterization is to develop a detailed description of the potential for health outcomes after exposure to the agent of interest during preconception or developmental lifestages. This begins with a description of each of the available studies (Section 4.1.2), considering critical windows of exposure and susceptibility, TK, TD, MOA, and dose-response information as well as the variability and uncertainty present in each study. The database is then synthesized from

the individual study evaluations, and the quality and quantity (i.e., the comprehensiveness) are characterized using a weight-of-evidence (WOE) evaluation (Section 4.1.3.1). This includes information about differences and similarities in experimental animal species versus humans regarding lifestage-specific TK and TD, the extent of the database for different lifestages, and lifestage-specific susceptibilities. The results of the hazard characterization are iterated with the dose-response and exposure analyses (Section 4.1.4) if indicated by the conclusions from summarizing the hazard database.

Finally, the lifestage-specific hazard characterization is summarized including a scientific rationale for the identification of relevant outcomes and susceptible lifestages based upon the data (Section 4.1.5). The identified outcomes and susceptible lifestages are further evaluated in the subsequent dose-response characterization step (Section 4.2). This information feeds into the comprehensive lifestage-specific risk characterization (Chapter 5).

Throughout the hazard characterization, relevance of the information to the overall goals of the assessment is considered. It may be appropriate to refine the conceptual model (Section 3.2) or analysis plan (Section 3.3) after thoroughly evaluating the available hazard data. For example, a conceptual model may focus on an exposure to a chemical or chemical class that results in thyroid tumors. Thyroid hormone is critical to development of the nervous system (Farwell et al., 2006; Pals et al., 2006; Ramos and Weiss, 2006; Santisteban and Bernal, 2005) and immune system (Bossowski et al., 2003; Lam et al., 2005). If development of these organ systems were not considered in the conceptual model for analysis of the chemical(s), then the conceptual model will need to be refined to consider the relevant critical windows of development.

Figure 4-3 illustrates a detailed approach to characterizing hazard from environmental exposures during development. More specific information on hazard characterization for developmental lifestage exposures can be found in the existing EPA risk assessment guidelines for developmental toxicity (U.S. EPA, 1991), reproductive toxicity (U.S. EPA, 1996), neurotoxicity (U.S. EPA, 1998b), and cancer (U.S. EPA, 2005b).

4.1.2. Qualitative Evaluation of Individual Studies

The objectives and scope of the risk assessment, defined in the problem formulation phase (Chapter 3), provide focus and a plan for identifying and examining all the relevant
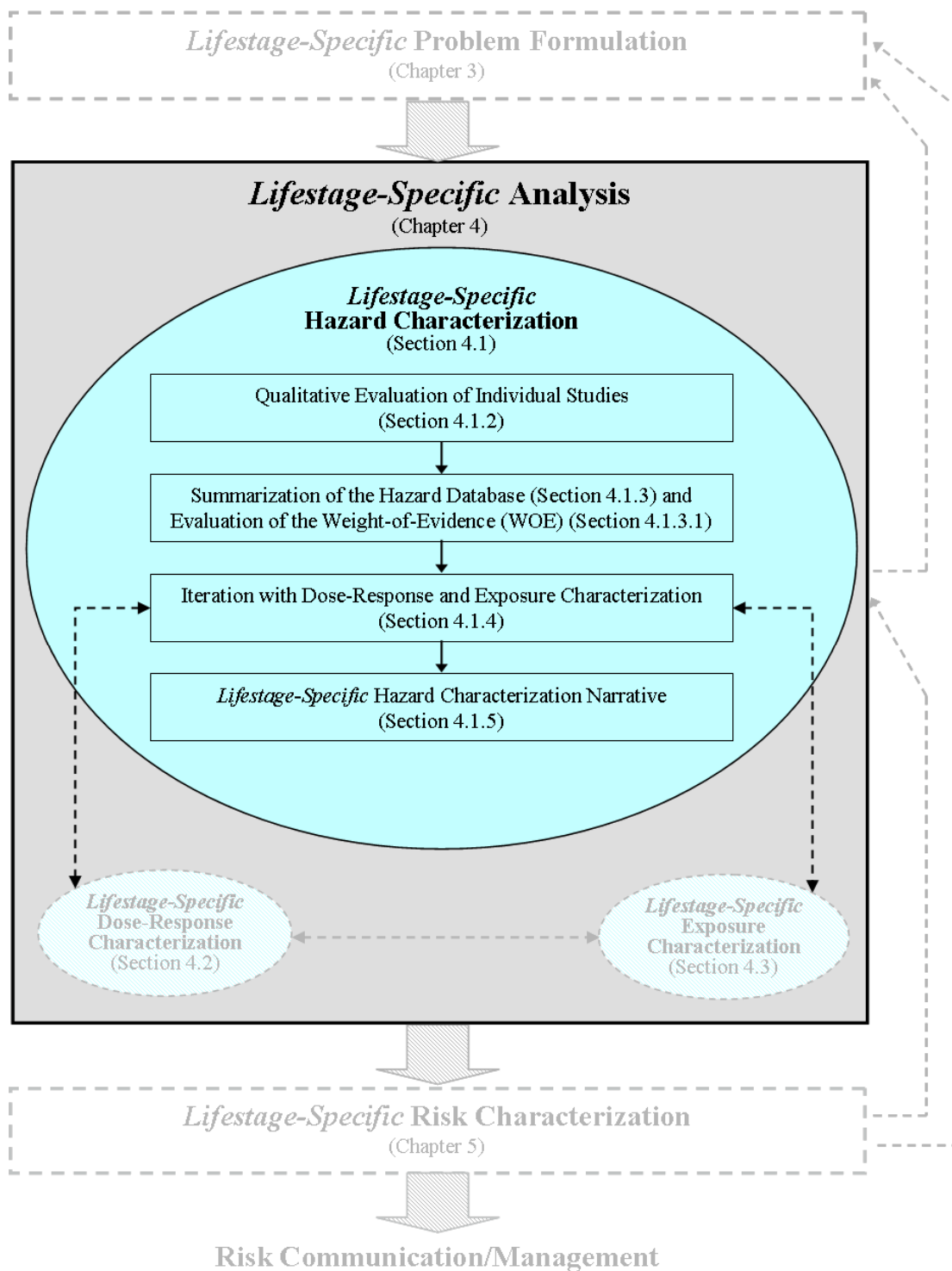
Figure 4-3. Flow diagram for lifestage-specific hazard characterization. The steps in hazard characterization include the evaluation of individual studies (Section 4.1.2), summarization of the hazard database (Section 4.1.3), an evaluation of the weight-of-evidence (Section 4.1.3.1), potential iteration with the other analysis steps (Section 4.1.4), and the hazard characterization narrative (Section 4.1.5). The dashed lines indicate where iterations may occur with other parts of the risk assessment process.

published human and experimental animal studies. A thorough qualitative evaluation of each study includes a complete description of the findings, an assessment of the study conduct and data quality, and a determination of sufficiency of data. To focus on risk from exposure to children, the evaluation process considers lifestage-specific information (pertaining to both the lifestage at which exposures occur and outcomes are observed) and issues within the overall context of the risk assessment. To assess study quality, the adequacy of the methods and results are characterized. In addition, it can be helpful to establish criteria for confidence in the evaluation and interpretation of the study findings that can be used later in the WOE evaluation (Section 4.1.3.1). The description of individual studies will contribute to the overall determination of the adequacy, strength, and completeness of the database for the characterization of hazard across lifestages. The following subsections describe topics to consider during the qualitative evaluation of each study, and example questions are addressed in Table 4-1.

4.1.2.1. *Study Purpose*

Describing the purpose of each study may provide information to evaluate the study as it relates to lifestages. For example, the study may be conducted in response to general risk evaluation issues, to explore an aspect of basic toxicology or biology, or to investigate a specific public health concern. The purpose of the study can range from hypothesis generation to hypothesis testing.

4.1.2.2. *Study Design*

A clear, concise description of the study design includes the number of subjects in each exposure group; descriptions of the study participants (e.g., gender, age); route, timing, and duration of exposure; and outcomes assessed. The timing of exposure and outcome assessment is important in relation to identifying and characterizing lifestage-specific risk. All of these are related to statistical power, which is further discussed in the WOE evaluation (Section 4.1.3.1). It is helpful to highlight strengths and weaknesses in the study design, particularly in relation to lifestage-specific assessments and how they may illuminate questions identified in the problem formulation (Chapter 3). For example, statistical power is a limitation that is often not discussed when studies are concluded to be "negative."

4.1.2.3. *Identifying Critical Windows of Exposure*

An evaluation of the exposures (or dosing/treatment to experimental animals) to the study participants involves characterizing the timing and duration of the exposures (e.g., exposure during preconception and critical windows of pre- or postnatal development) that have occurred across the lifestages of the study individuals. The timing and the duration of exposure to test substance in experimental animal studies could be informed by data on the critical windows of development of organ systems.

A useful source of information is the proceedings of a workshop on critical windows of exposure for children (Selevan et al., 2000), which addresses the respiratory and immune systems (Dietert et al., 2000; Holladay and Smialowicz, 2000; Peden, 2000; Pinkerton and Joad, 2000), the reproductive system (Lemasters et al., 2000; Pryor et al., 2000), the nervous system (Adams et al., 2000; Rice and Barone, 2000), the cardiovascular and endocrine systems (Barr et al., 2000; Hoet et al., 2000; Osmond and Barker, 2000; Sadler, 2000), and cancer/neoplasms (Anderson et al., 2000; Olshan et al., 2000). The WHO draft document, *Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals* (WHO, 2006) also reviews critical windows of development by organ systems.

4.1.2.4. *Outcomes Related to Developmental Lifestage Exposure*

A description of study findings, including the relationship of the outcome (both the outcome itself and timing of the outcome assessment) to the time of exposure, is a primary goal of hazard characterization. This includes an explicit consideration of outcomes at various lifestages due to exposure occurring during developmental lifestage(s). Developmental lifestage exposures may result in early or latent effects (Selevan et al., 2000; WHO, 2006). The evaluation of each study includes whether and how study outcomes address questions raised during the problem formulation phase (Chapter 3). For example, if the problem formulation specifically identifies a potential for risk after exposure to pregnant women in a residential setting, then it is important to carefully evaluate any available human and experimental animal data that examines outcomes following gestational exposures. Toxicities resulting from alteration of precursor events may be expected to be different depending on lifestage. Alteration of a precursor event in a mature animal or adult human may not have any significant health consequence, where the same precursor event alteration in a developing organism may have significant health consequences.

4.1.2.5. *Toxicokinetic Data*

All available lifestage-specific TK data are included and described in order to determine the relevance and impact of the TK data in evaluating the study and to determine the impact of exposure on response across lifestages. TK data can be used to verify that indirect exposure of the fetus or neonate (e.g., via maternal circulation or breast milk) occurred without relying on observable outcomes. In some situations, internal dose can be measured, providing greater confidence in derivation of the dose metrics (Section 4.2.2.3). If TK data are available across lifestages, this information can aid in highlighting key lifestages for the assessment. For example, immaturity of specific metabolic enzymes or renal capabilities (e.g., elimination) can result in a more or less toxic response in the young. Therefore, information on the developmental profiles of enzymes or organ systems can help identify particularly susceptible age groups.

Studies may find increased susceptibility of immature individuals but lack TK data to assist in the interpretation of these findings. In that case, default assumptions are generally applied. Three typical examples are (1) internal dose is equivalent to dose at the portal of entry, (2) the dose to the fetus is equivalent to the dose administered to the maternal animal, or (3) the internal dose to the immature individual is equivalent to that of adults. However, these default assumptions may not be health protective; therefore, the availability and use of TK data will likely decrease uncertainty in the risk assessment.

4.1.2.6. *Toxicodynamic Data*

TD data include information about the steps between the toxicant's first interaction with the target organ and the subsequent toxic outcome. Describing TD data for specific lifestages may provide corroborative evidence of potentially susceptible lifestages for a given chemical. For example, if TD information for a chemical suggests effects on the nervous system via decreasing luteinizing hormone and disruption of the hypothalamic-pituitary-gonadal axis, then greater concern would be warranted in cases when there are lifestage-specific TK data. This TK data may demonstrate that the chemical is found in the brain only during a developmental lifestage when the blood-brain barrier is not fully formed.

4.1.2.7. *Mode of Action Information*

Consideration of MOA information (key TK and/or TD steps) can be useful in

- understanding the susceptibility differences among various lifestages,
- determining the most appropriate experimental animal model for relevance to humans,
- determining when human exposure or outcome data during lifestages are limited or not available,
- predicting types of effects that might be seen during particular lifestages, and
- predicting potential susceptible lifestages.

For example, if a chemical has an anti-androgen MOA, *in utero* and peri-pubertal intervals might be sensitive exposure windows for male reproductive outcomes. Further, differences in androgen activity by lifestage can explain some of the observed differences in susceptibility; for example, for the pesticide vinclozolin (Anway et al., 2006; Euling and Kimmel, 2001). It is also possible that the MOA for a given chemical differs among lifestages; this is one possible explanation for differences in outcomes after exposures during developmental lifestages versus adulthood. For example, diethylstilbestrol (DES) produces reproductive, developmental, and carcinogenic outcomes after *in utero* exposure which are not observed following adult exposure (Herbst, 1987; Mericskay et al., 2005; Robboy et al., 1982). Also, organophosphorous pesticides inhibit cholinesterase throughout one's lifespan, but certain of these pesticide's inhibitory effects on neuronal differentiation and migration, which are attributed to an alternative, noncholinergic MOA, occur only during *in utero* and early postnatal neurological development (Campbell et al., 1997; Chakraborti et al., 1993; Dam et al., 1998; Young et al., 2005). However, chemicals with more than one MOA, such as methoxychlor, have been described (Chapin et al., 1997; Gaido et al., 2000; Gray et al., 1999a). Therefore, it is possible that the activity of the different MOAs may vary across lifestages.

4.1.2.8. *Qualitative Evaluation of Dose-Response*

A detailed qualitative evaluation of the lifestage-specific dose-response profile is useful, but not always available, when interpreting the outcome for individual studies. A well-characterized dose-response relationship helps support the judgment of whether an outcome is due to exposure during a specific lifestage. The shape of the dose-response curve may or may not be monotonic in nature.

These dose-response data are carried forward into the WOE evaluation (Section 4.1.3.1.3) because determining the relationship between adverse responses and exposures is achieved through consideration of the results in context of the other studies in the database and may highlight the importance of borderline or suggestive findings in individual studies and, ultimately, refine the interpretation of the data. For example, a prenatal developmental toxicity study in rats may identify a treatment-related malformation (e.g., spina bifida) that occurs with a demonstrable dose-response relationship; in a two-generation reproduction study, the interpretation of incidences of spina bifida that are observed in litters from treated groups may take on greater weight in the overall hazard characterization even in spite of the lack of significant incidence or a clear dose-response.

4.1.2.9. *Variability Analysis*

There are a number of sources of variability, both intrinsic and extrinsic, in human and animal toxicologic data. Intrinsic, or biological, variability includes heterogeneity across lifestages and is expressed to some degree in each parameter being measured. Examples of intrinsic variables in both human and experimental animal studies include age, gender, and genetic factors. On the other hand, the sources of extrinsic variability are external to the study individuals and can often be attributed to methodological considerations, to errors in study design, or to variations in implementation. Examples of extrinsic variables for experimental animal studies include handling techniques, ambient temperature, and noise. For epidemiologic studies, examples include variations in recruitment or data collection procedures.

Variability can be adequately characterized by the appropriate statistical treatment of individual study data. For example in developmental toxicologic studies, all pups in one litter are used as the unit of measure (n=1) to address issues of between-litter variability in response. High levels of variability may affect the ability to identify associations and make the interpretation of study data difficult. A detailed consideration of variability with appropriate analyses contributes to a determination of the adequacy, strength, and reliability of a study and its conclusions. Variability can be a source of uncertainty in the evaluation and interpretation of individual studies (Section 4.1.3.1.2). High variability can sometimes render a study uninterpretable within the context of the rest of the data or result in reduced confidence in the

veracity of the study findings, thereby decreasing the confidence placed in the study and its value for use in the WOE evaluation (Section 4.1.3.1).

4.1.2.10. *Uncertainty Analysis*

Uncertainty from a variety of sources in lifestage-specific data can affect the assessment of risk. Uncertainties can result from data gaps (i.e., missing information), inadequacies in the study protocol or methodologies, inaccuracies in the reporting of study findings, or inconclusive results. After a thorough consideration and description of the uncertainties for each study, any resulting assumptions, extrapolations, or speculative interpretations are described and utilized in the risk characterization (Chapter 5). Detailing data gaps helps provide an adequate characterization of the uncertainties of the risk from developmental lifestage exposure. For example, in laboratory animal studies, if the toxicologic evaluation characterizes adverse outcomes following exposures that traditionally occur throughout all developmental lifestages, then future study exposure methods may need to incorporate direct dosing techniques during specific lifestages (e.g., in pre-weaning or juvenile experimental animals) (Bruckner and Weil, 1999; Zoetis and Walls, 2003). In particular, experimental animal studies of exposure during the juvenile period specifically are rare, although they are increasingly becoming more common as they gain greater prominence in regulatory hazard characterization (Hurtt et al., 2004; U.S. FDA, 2006). Developmental (*in utero*) studies are more common but are not done for all chemicals and are limited because they do not involve direct dosing in postnatal life. One- and two-generation reproduction studies are also not conducted for all chemicals and are often limited in having postnatal dosing only via nursing and involve a limited number of outcomes (e.g., reproductive outcomes). Developmental neurotoxicity, developmental immunotoxicity, and other organ system-specific developmental studies also are not commonly performed and have limitations regarding the exposure route and apical outcomes/organ systems assessed. Due to the iterative nature of the evaluation process and the consideration of information from multiple sources, data from other human or experimental animal studies, data on structure-activity relationships (SARs), or TK or TD information, may be used to address uncertainties identified in a given study.

Table 4-1. Examples of lifestage-specific questions for evaluation of individual studies within hazard characterization.

Topic	Lifestage-Specific Question(s)
Study Purpose (Section 4.1.2.1)	Was the purpose of the study to address a lifestage-specific hypothesis or public health concern?
Study Design (Section 4.1.2.2)	Did the study design and methods address specific lifestages of exposure and their outcomes? What lifestages were assessed? How was lifestage/age measured?
	What were the strengths and limitations of the study design in assessing lifestage-specific exposure and outcome?
	For human studies, how did the methods impact the validity and reliability to determine children's exposure and outcome? Were lifestage factors (potential confounders) examined and accounted for, where appropriate?
	In experimental animal studies, was an appropriate route and matrix (e.g., vehicle, formulation, duration) of exposure employed across various lifestages? Were the dose range and levels appropriate across lifestages evaluated?
	Was the power of the study adequate to detect an effect after exposure during a specific lifestage? Were sample sizes, inclusion of both sexes, and animal litter numbers considered?
Identifying Critical Windows of Exposure (Section 4.1.2.3)	What is known about critical windows of exposure for the outcome and chemical?
	Were the routes of exposure relevant to the age-related exposure pathways for the age groups of interest? Did the exposure interval cover different lifestages, partially or completely?
	• What exposure/dose levels were assessed during the lifestage(s) of development? Were they the same across all the lifestage(s) identified in the study?
	• Were lifestage-specific behaviors discussed that could influence the exposure (e.g., maternal nurturing behaviors, offspring nursing or weaning activities, or exploratory/play behaviors in the immature individual)? If so, in what direction would the dose likely be affected?
	Was exposure verified for critical lifestages?
	• In animals, what was the route of exposure and was it the same throughout all lifestages? Did exposure occur across more than one developmental lifestage(s) in the study?
	• For humans, was there more likely to be exposure(s) from this source during certain lifestages than others? If so, would this be expected to affect the results of the study and was this accounted for in the study? Were other possible sources of exposure considered for various lifestages?
Outcomes Related to Developmental Lifestage Exposure (Section 4.1.2.4)	What was the timing of assessment of outcomes? Were outcomes dependent upon the exposures during critical stages of development? How were latent effects assessed?
	Were lifestage-specific outcomes assessed in the study (e.g., different outcomes during different developmental stages vs. adult stages)?
	What methods were used to assess lifestage-specific outcomes after developmental lifestage exposures? Were they appropriate? What were their limitations (e.g., were relevant lifestage-specific outcomes not assessed)?
	Were biological plausibility and internal consistency of findings considered for lifestage-specific data?
	Did the authors make lifestage-specific conclusions in the study, and what were their assumptions and interpretations?
TK Data (Section 4.1.2.5)	Are there lifestage-specific differences in absorption, distribution, metabolism (toxification or detoxification), or elimination assessed in the study? At varying doses?

TD Data (Section 4.1.2.6)	Are there TD data for the specific lifestage(s) that relate to outcomes?
MOA Information (Section 4.1.2.7)	For the outcome(s) assessed in this study, what is known about the chemical's MOA after exposure at different lifestages? Is there information suggesting similarities or differences in MOA for different lifestages of exposure?
	Have precursor events (e.g., biomarkers) been identified for a particular outcome? If so, were precursor events similar across lifestages? Are the toxicities resulting from precursor events expected to be different depending on lifestage of the outcome?
	Are outcomes related to the MOA relevant to the lifestages of concern in this study? Are there different MOAs suspected for different lifestages?
	If there are multiple outcomes described at differing lifestages, then are these consistent with one or more MOAs?
Qualitative Evaluation of Dose-Response (Section 4.1.2.8)	Are there lifestage-specific dose-response relationships assessed in the study? What are the similarities and differences in dose-response across lifestage of exposure?
	What is the shape of the dose-response curve for lifestage-specific toxicologic outcomes?
Variability Analyses (Section 4.1.2.9)	What was the variability in the control data for parameters of normal growth and development and other outcomes for the lifestage of interest?
	Was this variability in measures within expected ranges? If not, could this mask detection of an outcome?
Uncertainty Analyses (Section 4.1.2.10)	Are there any lifestage data gaps or uncertainty considerations (i.e., were some lifestages exposed and/or assessed, while others were not)?
	Were critical windows of exposure and associated outcomes adequately addressed?
	Were lifestage-specific studies conducted with appropriate quality laboratory practices and standards (e.g., Good Laboratory Practice) (U.S. FDA, 1978)?
	Did the conduct of the study result in uncertainties in findings that are particularly pertinent to lifestage-specific data interpretation? Were any inadequacies in the data lifestage specific?

4.1.3. Summarization of the Hazard Database

After summarizing the relevant studies for the lifestage-specific hazard database (Section 4.1.2), the exposure-response array is assembled and then evaluated. Not all summarized studies judged may be useful to the risk assessment (NRC, 1994). Well-justified decisions to include or exclude a study are provided in the hazard narrative (Section 4.1.5).   The adequacy of studies and characterization of the database are discussed in detail in *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002a, Section 4.3).

The overall hazard database includes detailed descriptions of all available studies relevant to and critical for evaluating the hazard to children, specifically those with developmental exposures, effects, or outcomes. The database may also include *in vitro* data, MOA or mechanistic studies, and toxicity data in adults to help profile the toxicologic response in children, or the database may provide support for assumptions made during the hazard characterization. A careful review of the studies' exposure durations and lifestages may help to

determine the relative importance (weight) of the studies when estimating potential risks to children. Issues to consider include the pathways (including media and route), and whether they are relevant to children; the intervals of exposure, and whether they included critical lifestages; and issues suggestive of differential susceptibility of children or specific lifestages.

A detailed characterization of the study outcomes is also important for the characterization of the database. Often, the structure and presentation of data summaries are driven by the outcome data. Common links are examined across studies. For example, for one chemical with detailed MOA information, the summary could focus on hazard in relation to that MOA and what the MOA may predict about potential critical windows. For other chemicals, the description might focus on specific developmental outcomes, target organs, or susceptible lifestages. The emphasis of the hazard summary is on the relationships (i.e., patterns) across observed outcomes, in relationship to lifestages and MOA. For some chemicals, only very limited human or experimental animal hazard information may be available. However, detailing the lack of information about an agent (i.e., data gaps and uncertainties) is crucial to an adequate characterization of risk to children from environmental exposures.

4.1.3.1. *Evaluation of the Weight-of-Evidence of the Hazard Database*

During the evaluation of the hazard database, the major strengths and weaknesses of the available relevant data are identified and are summarized in the WOE evaluation. The WOE evaluation includes expert judgment of the completeness of the database. For this Framework, key themes were adapted to meet the needs of evaluating human and toxicologic studies relevant to children's health risk assessment. These key themes include temporality, strength of the association, qualitative dose-response relationship, experimental evidence, reproducibility, biological plausibility, alternative explanations, specificity, and coherence (Figure 4-4) (Hill, 1965; Gray et al., 2001; Seed et al., 2005; U.S. EPA, 2000c, Chapter 4; Vineis and Kriebel, 2006; Weed, 2005). Criteria for evaluating the key themes for the WOE may be developed during problem formulation (Chapter 3) to address specific assessment needs. The adequacy, strength, and completeness of the entire database are considered. The description of the database includes a qualitative exposure-response array, data gaps, uncertainties, and assumptions that are summarized in the hazard characterization narrative (Section 4.1.5).
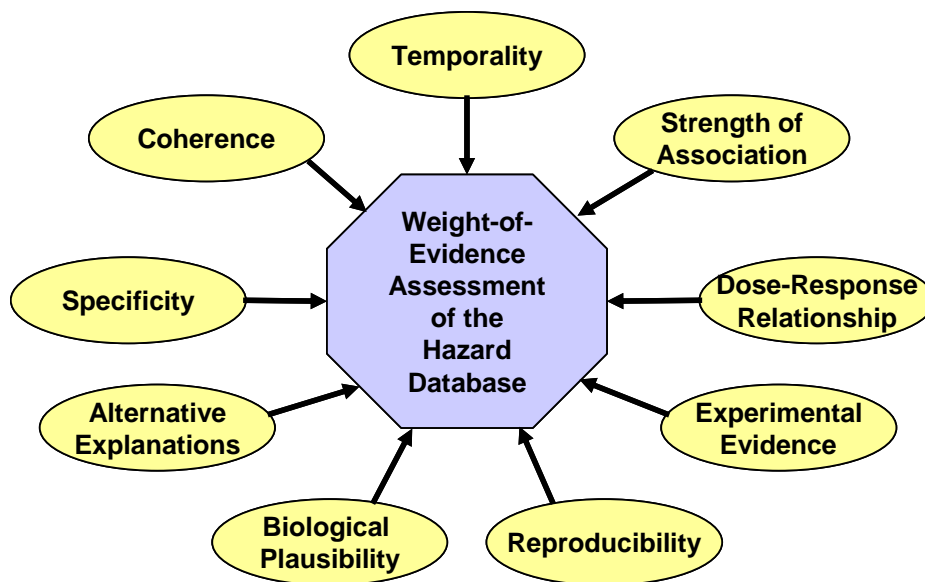
Figure 4-4. Conceptual view of a WOE evaluation. This figure illustrates the considerations within a WOE evaluation of toxicity data. The relative weight of each consideration will vary for each assessment.
Source: Adapted from Hill, 1965; Gray et al., 2001.

The principles developed by Hill (1965) focused on evaluating human studies, while Gray et al. (2001) focused on evaluating animal toxicology studies (Figure 4-4). Further details about EPA's WOE evaluation approach can be found in the *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994), *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b), *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002a, Section 4.3.2.1), and *Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment* (U.S. EPA, 2002d, Section III). The following subsections describe the key themes that can be considered in the WOE evaluation, and example questions are presented in Table 4-2.

4.1.3.1.1. *Temporality.* Temporality is the basic premise that the exposure must occur prior to the outcome (U.S. EPA, 2002a, pp. 4-13 to 4-14). For developmental lifestage-specific data, temporality includes consideration of the relationship between the timing of exposure and outcome. Depending on what is known about potential critical windows of exposure (Section 4.1.2.3), more or less credence may be given to the association with the observed outcome. When developmental lifestage-exposure data exist, the temporal relationship between the

exposure and outcome(s) may be assessed. Further, when there are data that provide an accurate characterization of the timing of the exposure and outcome, the latency time between the exposure to the outcome may be determined. For example, exposure to dibutyl phthalate (DBP) during late gestation leads to a number of male reproductive developmental effects (e.g., decreased anogenital distance, increased nipple retention, and hypospadias) that are observed at different stages of development in the rat (Barlow and Foster, 2003; Gray et al., 1999b; Mylchreest et al., 1999, 2000).

4.1.3.1.2. *Strength of the association.* Greater weight is generally given to more rigorous studies as well as those with higher statistical power, and therefore, greater statistical precision. Strength of the association considers both rigor and statistical power. Rigor is the degree of proper design, conduct, and analysis of a study. It can be difficult to determine rigor because in some cases, study methods presented in published studies lack sufficient detail. Additionally, rigor is not simply equivalent to conduct under GLP regulations for nonclinical laboratory studies (U.S. FDA, 1978). Many older studies showing early-lifestage sensitivity to carcinogens were rigorously conducted, but before the GLP regulations were first published in 1978;[3] similarly, many rigorous studies in academic institutions do not follow GLP regulations. Statistical power is the ability of a study to detect effects of a relevant magnitude and relates to the sample size, the number of data points, the stratification of findings, and the background rates of the specific outcome(s).

For the evaluation of human studies, the strength of an observed association may be affected by the presence of uncontrolled or unmeasured confounders, the prevalence of effect modifiers in the study population, or bias. A confounder is a variable that can cause or prevent the detection of a change in an outcome of interest and is not an intermediate variable on the causal pathway between exposure and outcome but is associated with the factor under investigation. A confounding factor can often be controlled for or accounted for in the statistical analysis. An effect modifier is a variable that modifies the outcome of interest by a greater (synergistic or additive) or lesser (antagonistic) effect. An effect modifier can sometimes be identified through stratification of the data. Many effect modifiers and confounders are

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[3] There are different GLP citations for U.S. FDA and U.S. EPA (including for FIFRA and TSCA). These have been updated several times over the years.

potentially lifestage specific, and whether and how these have been evaluated in the data analysis could affect the study outcomes or interpretation of study results. A lifestage-specific example of a confounder is maternal socio-economic status (SES), which can influence or bias the interpretation of the offspring's cognitive development. For animal toxicology studies, a lifestage-specific example of an effect modifier is maternal health status, such as maternal or offspring nutrition, which can influence the development and maturation of the young (Cappon et al., 2005; Fleeman et al., 2005). Another example is the timing of heat exposure and effects on skeletal development in the rat (Cuff et al., 1993; Kimmel et al., 1993).

4.1.3.1.2.1. *Variability analysis.* The sources of variability within individual studies (Section 4.1.2.9) are also important factors for the interpretation of the dataset. They can contribute to overall uncertainties in the database, including those uncertainties that are applicable to the lifestage-specific hazard characterization. Variability of response across studies and possible reasons for the variability are assessed and considered when developing an exposure-response array. For example, in animal studies the response variable could vary among studies performed when using different strains of the same experimental animal species or when studies are performed in different decades, possibly due to genetic drift in laboratory animal populations (Hartl, 2001; White and Lee, 1998).

4.1.3.1.2.2. *Uncertainty analysis.* In the evaluation of individual studies (Section 4.1.2), data gaps (missing information) may be identified that could impact the quality of the study, and these are considered in total when evaluating the database. In addition, when combining the data from all the studies, data gaps for the comprehensive database of information on the chemical can be assessed. For example, the combined studies may have assessed outcomes after exposure during all developmental stages except for the peri-pubertal period. If this were the case, then a data gap in coverage of this particular developmental lifestage of exposure would be noted. For any chemical assessment, there will be inevitable gaps in the available lifestage-specific information; it is the relative impact of missing or inadequate information to the overall goals of the assessment that are to be judged. In some cases, information gleaned from the toxicologic profiles of structurally-related chemicals or chemicals with a similar MOA can assist in interpreting the relative importance of a data insufficiency. Sometimes this information can

provide a way of bridging a data gap (Julien et al., 2004). When evaluating lifestage-specific uncertainties and data gaps, study design (e.g., measurements, exposure, and outcomes across lifestages) is addressed (U.S. EPA, 1991, Section 3.1.2.1; U.S. EPA, 1996, Section 3.3.1.5; U.S. EPA, 2002a, Section 4.3.1). The characterization of data gaps also includes a determination of whether required toxicologic studies (i.e., by statute or convention) are present (e.g., a rodent and a non-rodent prenatal developmental toxicity study, and a reproduction and fertility effects study).

Uncertainties arising from the absence of any other relevant data identified are addressed. The potential qualitative and quantitative impact of these missing data on the risk assessment (e.g., on the point of departure [POD]) is considered and may be useful in determining the magnitude of a database uncertainty factor (UF) during dose-response characterization (U.S. EPA, 2002a) (Section 4.2.4.4). Additionally, information from the exposure characterization (Section 4.3) could be useful when identifying any remaining uncertainties in the hazard characterization. For example, if the exposure characterization identifies a high potential of exposure to nursing infants, specific TK data on milk partitioning may be deemed particularly important in the risk assessment, and absence of these data could be considered an important source of uncertainty. Finally, the level of confidence in the final risk estimates is based on a detailed description of the assumptions and interpretations of the uncertainties in the overall database.

Sometimes, other types or sources of data can assist in satisfying an identified data gap or uncertainty. For example, if for a chemical being evaluated, there are no data relevant to the hazard characterization following exposure during a particular lifestage, data from a similar lifestage exposed for a different chemical that has been shown to produce the same active metabolite might be useful in informing the assessment and reducing uncertainties relevant to this data gap.

4.1.3.1.3. *Qualitative dose-response relationship.* The dose-response relationship demonstrates a predictable change in an effect as a function of exposure/dose. Studies that directly relate the exposure/dose to the degree of the effect (i.e., increasing dose results in increasing effects) give stronger weight to the evidence (exposure-response array). For example, an association between increasing blood lead levels and a lower IQ in children has been reported (Canfield et al., 2003).

In some cases, the failure to observe a dose-response relationship may be due to the choice of dose levels or dose spacing in given studies, to a threshold effect, or to a more complex (e.g., a U- or J-shaped) dose-response relationship. Also, an observed dose-response relationship may, in fact, be related to a confounder, if that confounder has a direct response on the effect, and may be associated with the exposure at higher doses but not at lower doses. This is further discussed in the hazard characterization narrative (Section 4.1.5) and the dose-response characterization (Section 4.2).

4.1.3.1.4. *Experimental evidence.* Experimental evidence is provided with hypothesis testing. This hypothesis testing includes manipulation of the exposure scenario with resulting alterations in the response or response rate of outcomes. Hill (1965) defined *experimental evidence*, as evidence that removal of the exposure or supplementation with an antidote leads to a reversal of the outcome. Experimental evidence or hypothesis testing would include manipulation of the exposure scenario with resulting alterations in the response or response rate of outcomes. For some agents, this concept can apply to a lifestage assessment. For example, cases of exogenous estrogen exposure in prepubertal boys can lead to gynecomastia (male breast development) that can be reversed after removal of the estrogenic agent (Edinin and Levitsky, 1982; Felner and White, 2000). However, for other agents, removal of the exposure after the critical window has passed may not result in a reversible effect. In addition, effects may not occur when the exposure occurs outside of a given critical window. If studies exist that demonstrate a particular exposure during a defined critical developmental window, then this could constitute experimental evidence of the importance of that critical window of exposure. For example, prenatal thalidomide exposure leads to altered limb bud development (Stevens and Fillmore, 2000), and prenatal alcohol exposure can result in the irreversible outcomes related to fetal alcohol syndrome (e.g., facial dysmorphogenesis, cognitive deficits, Rubert et al., 2006; Yelin et al., 2005). If there is a hypothesized MOA, *in vitro* or transgenic animal models (e.g., knock-out, knock-in, conditional expressors) may add further weight and experimental evidence to a hypothesized association.

4.1.3.1.5. *Reproducibility.* Reproducibility, also termed *corroboration* by Gray et al. (2001), means that specific effects are seen under varied conditions. In the case that a lifestage-specific

effect is consistently observed in similar studies, under varied conditions, in multiple laboratories, across species, and by various routes of exposure, stronger weight can be placed on the chemical's association with the effect since it is less likely that biases or confounding factors are responsible for the results. However, inconsistent findings may be notable. For developmental toxic agents, exposure occurring during only one specific lifestage, but not all developmental exposures, may result in the outcome of concern. What may appear as a lack of reproducibility may actually be the result of disparate study designs examining different critical windows. Therefore, caution is warranted in dismissing seemingly inconsistent findings without careful consideration.

4.1.3.1.6. *Biological plausibility.* Biological plausibility is the determination of whether an observed outcome could be attributed to the toxicologic insult, given the currently known science. Biological plausibility may be informed by such things as available information on the biologic mechanism of a toxic response or on TK and TD similarities and differences across species or strains or for various lifestages. Some differences in sensitivity between different rodent strains have been found (Spearow et al., 1999, 2001). A toxic response observed following developmental lifestage exposure may be different from the response after exposure to an adult, and the response may be explained by critical windows of susceptibility. Cross-species and cross-strain similarities or differences in developmental windows of exposures may impact comparison for the database as a whole. For example, certain prenatal stages in humans are comparable to certain postnatal stages in rodents. However, when intra- or interspecies lifestage-specific data are lacking, a default assumption that exposure during any lifestage in experimental animals causes similar effects in humans is often applied. Another default assumption is that a response observed in experimental animals is expected to occur in humans (U.S. EPA, 1991, 1996, 1998b, 2005a,b). Defining these assumptions and the uncertainties that they address is a key part of the WOE evaluation and the identification of data needs.

To move towards more quantitative interspecies comparisons will require a better understanding of developmental biology and ontogeny of different organ systems. Several relevant papers comparing organ and system development across species are available for reference (Hattis et al., 2004, 2005; Hurtt and Sandler, 2003a,b; Selevan et al., 2000). Comparison of specific physiological systems include the female (Beckman and Feuston, 2003)

and male (Marty et al., 2003) reproductive system, the cardiac system (Hew and Keller, 2003), the immune system (Holsapple et al., 2003), the central nervous system (Wood et al., 2003), the gastrointestinal system (Walthall et al., 2005), the renal system (Zoetis and Hurtt, 2003a), the respiratory system (Zoetis and Hurtt, 2003b), and osteogenesis (Zoetis et al., 2003).

4.1.3.1.7. *Alternative or multiple explanations.* One must consider and clearly articulate other explanations for the observed outcome(s) after the exposure of interest. It is important to consider whether these explanations are consistent with the database. Reasons for null findings must also be examined. Alternative hypotheses may also explain similar findings. If other hypotheses can be ruled out, then more weight can be given to the principal hypothesis or alternative hypotheses defined in problem formulation (Chapter 3). For example, a non-mutagenic MOA could be considered as an alternate explanation to the primary hypothesis of a mutagenic MOA leading to childhood leukemia. In another example, decreased pup body weight in a two-generation reproduction study may be the result of direct toxicity to the pups at a susceptible lifestage, or alternatively, the toxicant may be interfering with lactation in the dams, thereby depriving the pups of nutrition needed for normal growth. These alternative explanations could have very different implications for judgments about children's risk. This information is also discussed in the risk characterization when considering explanations for alternative risk estimates (Section 5.1.6).

4.1.3.1.8. *Specificity.* Specificity, as discussed by Hill (1965), entails a single cause and effect relationship resulting from exposure to an environmental agent. It may be difficult to define such a relationship for developmental outcomes since the alteration of organizational events may be altered during development and thus may lead to multiple outcomes, depending on the critical window of exposure (Barker hypothesis, Lau and Rogers, 2004). Evaluating specificity of a particular MOA, with regard to both the timing of exposure and individual outcomes, presents a challenge in part because so much time elapses between the occurrence of exposure and latency of expression of an outcome (Section 4.1.3.1.1). Specificity is defined within the context of this document as a determination of the relationship between one exposure, the effect(s), and whether each effect is mediated through a single or alternative MOAs. Exposure during a critical window may lead to several adverse outcomes; alternatively, the MOA may be unique for developmental

lifestage exposures when compared to later lifestage exposures. Similarly, the effect of one agent may vary depending on differences in critical windows of development for the target tissue or organ.

4.1.3.1.9. *Coherence.* Coherence summarizes all the principles discussed above and discusses the extent to which the data are similar in outcome and exposure/dose and whether they support each biologically plausible hypothesis or MOA. An observed association is given more weight when it is consistent across the database. This relates to both reproducibility (Section 4.1.3.1.5) and biologic plausibility (Section 4.1.3.1.6). An example of coherence is the observance of treatment-related increases in total resorptions at cesarean section in a prenatal developmental toxicity study and the corollary observation of reduced litter sizes at parturition in a two-generation reproduction study. Relating the existing database to the larger toxicologic database about structurally related chemicals or chemicals with a similar MOA can be useful to address coherence and bridge some data gaps. For example, for one chemical with detailed MOA information, the summary could focus on hazard in relation to that MOA and what the MOA may predict about potential critical windows. For other chemicals, the description might focus on specific developmental outcomes, target organs, or susceptible lifestages. SARs with other chemicals or chemical classes may be explored to determine the extent to which these data can inform the assessment via an MOA discussion or to help reduce uncertainties.

Table 4-2. Examples of lifestage-specific questions for evaluation of the WOE of the hazard database.

Topic	Lifestage-Specific Question(s)
Temporality (Section 4.1.3.1.1)	To what degree were the timing of exposures described, including the exposure level and the lifestage of exposure?
	Do time-course data exist following developmental lifestage exposures?
	Within the hazard database, are exposure intervals or timing of outcome assessments missing that are necessary in describing the relationship between the exposure and outcome timing?
Strength of the Association (Section 4.1.3.1.2)	How sufficient is the database for evaluating developmental lifestage exposure?
	Are the lifestage-specific data of adequate quality? Do the adequate quality studies comprise a database of adequate quantity?
	Did the relevant studies have sufficient statistical precision for confidence in the results?
	For human data, to what degree were confounding factors, effect modifiers, and other risk factors considered? Were the major demographic and other personal/community characteristics examined (e.g., age, sex, ethnic group, socioeconomic status, smoking

	status, occupational exposure)? To what degree were biases considered?
	Variability Analysis
	What sources of variability have been identified in the lifestage-specific database? What effect does this variability have on the interpretation of the lifestage-specific database?
	Uncertainty Analysis
	What are the significant data gaps in the database with regard to children's risk?
	• Which lifestages of exposure were assessed? Did exposure occur throughout all critical lifestages? Were relevant lifestage pathways of exposure and exposure intervals evaluated? Were there developmental stages during which exposure was intermittent or did not occur. What was the potential impact of any gaps in exposure? Were lifestage-appropriate biomarkers of exposure assessed?
	• Were all critical outcomes evaluated across lifestages? Have appropriate organ systems, tissues, and outcomes been adequately assessed for all lifestages of concern? Were lifestage-appropriate biomarkers of outcome assessed?
	• Does the extent of the database for risk from children's exposure indicate the need for follow-up studies to better define uncertainties for the specific assessment question and issues?
	What are the resulting uncertainties in the database with regard to children's risk?
	• Have any uncertainties in developmental exposure been identified?
	• Have any uncertainties in internal dose estimation been identified following developmental exposures (e.g., are there TK data that support the study design and the interpretation of the data for critical lifestages)?
	• Did the conduct of the studies in the database result in uncertainties in findings that are particularly pertinent to lifestage-specific data interpretation? Were some studies or data excluded on the basis of poor quality?
	Can information from the comparison of structurally related chemicals, or chemicals with a similar MOA with lifestage-specific data, be used to modify the impact of identified uncertainties or data gaps?
Qualitative Dose-Response Relationship (Section 4.1.3.1.3)	What is the nature of the dose-response relationship for developmental exposures and outcomes at all lifestages? What is the shape of the dose-response curve?
	Are there differences seen in dose-response curves for the same outcome between studies? Could confounding factors explain these differences?
	Are there differences in dose-response curves for specific lifestages?
Experimental Evidence (Section 4.1.3.1.4)	Has the hypothesized critical window of exposure been supported by additional epidemiologic data in humans or experimental evidence in animals?
	Do alterations or differences in exposure paradigms result in alterations in outcome?
Reproducibility (Section 4.1.3.1.5)	Were the findings examined for consistency within and across studies, laboratories, species, and strains?
	Could inconsistencies in findings be explained by differences in exposures during a critical window of development?
Biological Plausibility (Section 4.1.3.1.6)	If there are lifestage-specific findings, were they examined for biologic plausibility?
	Are there temporal differences between experimental animals and humans for the lifestages when exposures or specific outcomes occur (i.e., what are the comparable developmental events among the species and strains)?
	Are there any cross-species differences in developmental windows of exposures that impact comparison for the database as a whole?
	Was dosing/exposure during potential or known critical windows of exposure identified for both humans and experimental animals? Is the dosing route used for

	animals relevant to human exposure?
	Is the dose-response relationship seen in experimental animals at doses that are relevant to exposure at developmental lifestages in humans (i.e., environmental levels)?
	Are there any interspecies similarities or differences of effects for comparable lifestages of development?
	Are there any intraspecies (e.g., cross-strain) concordance of effects at lifestages of development? If not, are there underlying biological reasons to explain these differences?
	What are the key toxicologic and epidemiologic studies that provide the basis for health concerns following children's exposures? Do other valid studies support or contradict these findings? Are negative studies considered?
	What adverse outcomes at the lowest exposure levels were observed, and what is the basis for these observed outcomes? Have precursor events/biomarkers or the MOA been identified?
	Besides the developmental lifestage effects observed in the key studies, are there other health outcomes of concern?
	Have the appropriate studies been performed (within the database or elsewhere) to determine critical windows of exposure? If so, what are they? Did exposure intervals include known or suspected critical windows?
Alternative or Multiple Explanations (Section 4.1.3.1.7)	Should some data or studies be eliminated from consideration or inclusion in the WOE evaluation?
	To what degree were alternative explanations considered?
	Are studies with null findings considered?
	Are alternative hypotheses considered that might explain the observed lifestage-specific outcomes? Does an alternative hypothesis better explain the data than the primary hypothesis?
Specificity (Section 4.1.3.1.8)	Is there a specific outcome associated with a specific lifestage exposure?
	Are there multiple outcomes that manifest after developmental lifestage exposures? Can these be explained through a common MOA?
Coherence (Section 4.1.3.1.9)	Was a meta-analysis performed to combine epidemiologic or toxicologic studies?
	Do the data provide information about lifestage susceptibility? Is the relationship consistent across lifestages or specific to exposure during one or more lifestages?
	What types of human studies are available (e.g., case-control, cohort or human ecologic studies, or case reports or series)?
	Assuming relevant exposure routes considered for specified lifestages, were study results consistent?
	Could differences in pathways and intervals of exposure explain differences in study results for relevant lifestages?

4.1.4. Iteration with Dose-Response and Exposure Characterization

The information gathered in this hazard characterization step will subsequently be used in the dose-response characterization step (Section 4.2). For example, if there are data from the exposure-response array (e.g., no-observable-adverse-effect-levels [NOAELs], lowest-observable-adverse-effect-levels [LOAELs], benchmark doses [BMDs], BMD lower confidence limits [BMDLs]), or data supporting other quantitative approaches like quantitative risk

estimation (QRE), then this information is subsequently considered in dose-response characterization.

For human studies, consideration of and coordination with the exposure characterization step (Section 4.3) is helpful at this point in the process and can provide important context for the evaluation of the hazard outcomes, characterization of uncertainties, and identification of further testing or research needs.

4.1.5. Lifestage-Specific Hazard Characterization Narrative

In this final step in the hazard characterization, a scientific rationale for the selection of outcomes is clearly and concisely summarized. Included are considerations of lifestage-specific outcomes, including susceptibility of individuals, the impact of interindividual variability on response, and remaining uncertainties in the hazard evaluation. Lifestage-relevant outcomes in the lower dose ranges are described for use in the quantitative dose-response characterization (Section 4.2). For example, different low-dose ranges (e.g., NOAEL; LOAEL) may have been identified for different outcomes or for different lifestages of exposure, depending upon the routes and durations of exposure. The hazard characterization information is also combined with the exposure characterization information (Section 4.3) to determine a risk characterization that includes components for describing lifestage-specific risks (Chapter 5).

The report *A Review of the Reference Dose and Reference Concentration Processes* recommends summarizing the extent of the database by describing it as a continuum from a *minimal* to a *robust* database (U.S. EPA, 2002a, pp. 4-19). These terms define the continuum of database characteristics, with *minimal* describing the least amount of information that would be sufficient to conduct a risk assessment, and *robust* including data that fully characterize the potential toxicity of a chemical or group of chemicals. The intent is for the assessors to characterize and justify the extent of the database in a narrative form, including variabilities, data gaps, and uncertainties (e.g., lifestage-specific exposures and outcomes, TK and TD data, the types of outcomes evaluated and lifestages of assessment of outcomes, reversibility of effect, and latency to response) that aid in determining the extent of the database.

The lifestage-specific hazard characterization narrative includes thorough assessment of the overall variabilities (Section 4.1.3.1.2.1), uncertainties, and data gaps (Section 4.1.3.1.2.2) that have been identified in the database, both generally and specifically for evaluation across

lifestages. For example, well-justified decisions to include or exclude a given study from the database or exposure-response array are explicitly stated. The emphasis of the hazard summary is on the relationships (i.e., patterns) across observed outcomes in relationship to lifestages and MOA. Often, the structure and presentation of the summaries are driven by the outcome data. The database may also include *in vitro*, MOA, and exposure data and toxicity data in adults that help profile the toxicologic response in children or provide support for assumptions made during the hazard characterization. Following are some overarching questions to ask in the hazard characterization narrative:

- What are the lifestage-specific outcomes from the whole database that were identified in the lower dose range(s) (not just a single "critical effect")? What are the lifestage-specific outcomes relevant for use in quantitative dose-response characterization?

- What are the most susceptible lifestages for exposure (e.g., women of childbearing age [preconception and fetuses], breast feeding infants, toddlers or older children) from the available data? Is there justification for the most susceptible lifestage(s) provided by the data to support the relevant outcomes of concern?

4.2. LIFESTAGE-SPECIFIC DOSE-RESPONSE CHARACTERIZATION

4.2.1. Introduction

Ideally, the adverse health effects identified in the hazard characterization (Section 4.1) are linked to relevant environmental exposure predictions (Section 4.3) through a dose-response characterization. The nature and number of risk estimates is governed by the problem formulation (Chapter 3), hazard characterization (Section 4.1), and the available data. A lifestage-specific dose-response characterization (Figure 4-5) begins with the summary of the available data from the hazard characterization (Section 4.1) to conceptualize a MOA, to select dose-response models, and to apply extrapolations and derive risk values. Variability, sensitivity, and uncertainty are analyzed, and the results of the entire analysis are iterated, if necessary, with the hazard and exposure characterizations. The dose-response characterization culminates with a descriptive narrative of the data, models, estimates, and uncertainties applied in the dose-response estimate.

Consideration of differences in both human and experimental animals for routes and durations of exposure, TK and TD processes, and outcomes helps inform the selection of the
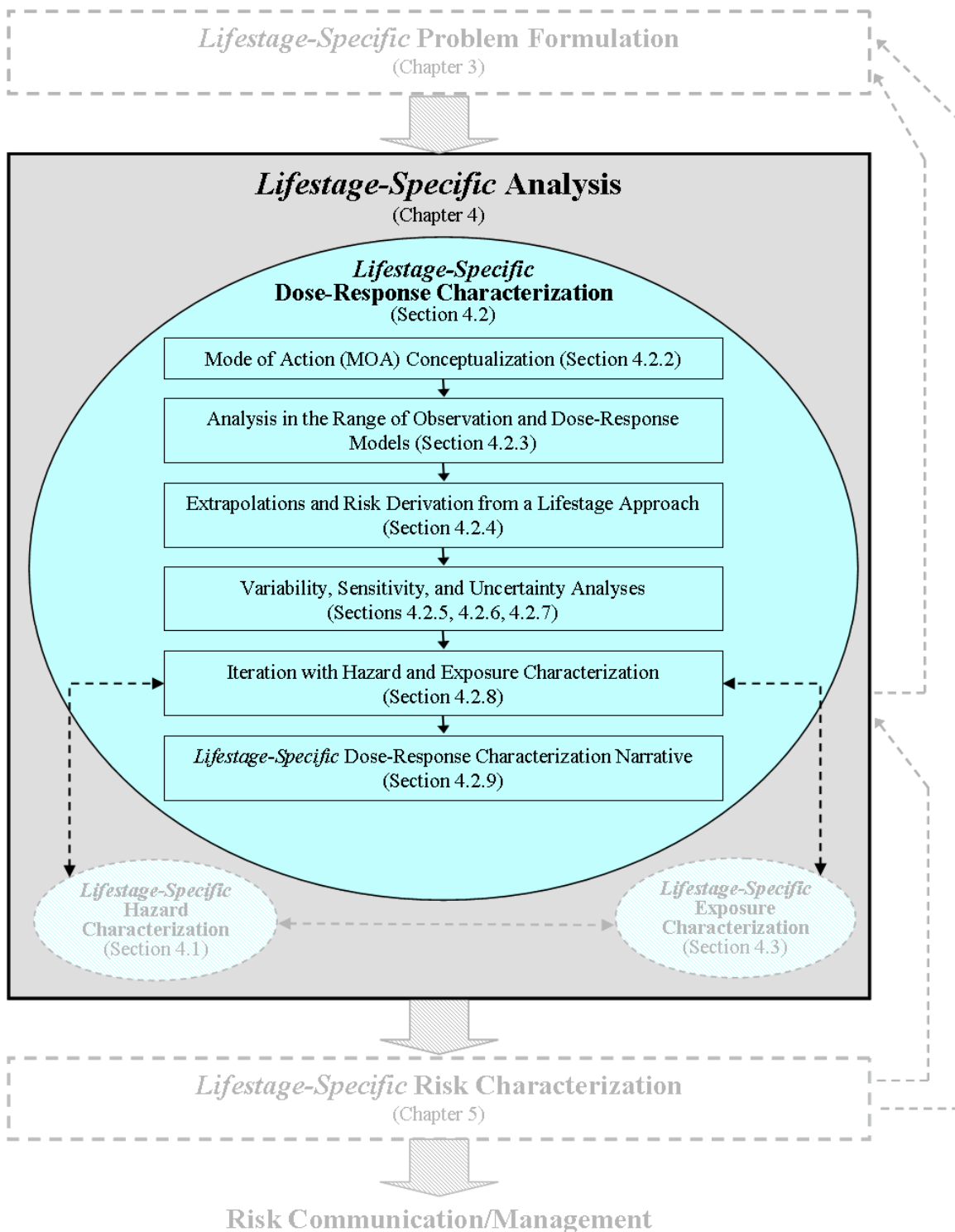
Figure 4-5. Flow diagram for lifestage-specific dose-response characterization. In the lifestage-specific dose-response characterization, a selection is made for the dose-response relationships for lifestages of interest based on input from the hazard data (Section 4.1) and the exposure data (Section 4.3). Appropriate extrapolations and risk value derivations are performed and described in the dose-response characterization.

most appropriate dose-response data and models for a given assessment. In the past, different analytical approaches have been used, depending on whether the outcomes were cancer or noncancer effects. More recently, there has been a recognition within the scientific community that the traditional dichotomy of cancer versus noncancer dose-response characterization is problematic, and approaches for characterizing outcomes to have either threshold (i.e. nonlinear) or non-threshold (i.e., linear) responses based upon their MOA(s) have been proposed (Bogdanffy et al., 2001). This *harmonized* approach recognizes that both cancer and noncancer outcomes can appropriately be characterized as threshold or non-threshold when data are available to support this selection.

Based on the problem formulation for a given risk assessment, an approach for carrying out a dose-response characterization is developed. As described in the problem formulation (Chapter 3), the scope and breadth of an assessment are established and generally fall into two categories, narrow and broad. The narrow or broad focus of the problem can restrict the dose-response characterization to more defined approaches. Regardless of the breadth of the assessment, the exposure scenario, or the hypothesized MOA of the environmental agent, the lifestage approach can add to the overall soundness and confidence in the assessment.

Dose-response values are typically categorized by route (oral, dermal, inhalation) and duration of exposure (acute, short-term, chronic). For instance, reference dose (RfD) and reference concentration (RfC) values can be calculated for various routes and durations of exposure (U.S. EPA, 2002a). Acute, short-term, and subchronic exposures are of particular concern because embryogenesis and prenatal, neonatal, and postnatal development provide ample opportunities for toxicant exposures to alter the regulation of development, which may lead to qualitatively different outcomes than equivalent exposures in adults.

Perhaps less apparent, however, is the applicability of long-term, or chronic, risk values to children. Although reference values (RfVs) derived from adult data are thought to be health-protective of sensitive populations (due to the application of intraspecies and database UFs), children may be chronically exposed to environmental toxicants. Chronic exposure is defined as exposure up to 10% of lifetime; therefore, seven years of exposure meets the EPA definition of chronic human exposure (U.S. EPA, 2002a). Thus if data suggest that a developmental lifestage is the most sensitive and sufficient data are available, an RfV could be derived from this

lifestage. In this derivation, the magnitude of the intraspecies and database UFs may be different than if the RfV were derived from adult data.

Unit risk estimates such as cancer slope factor (CSF) and inhalation unit risk (IUR) are used to define the exposure concentration that yields a given level of risk during a lifetime (e.g., 1×10^{-6}). Although the latency of time to tumor may mask detection of cancer from exposures occurring in developmental lifestages, early exposures may indeed increase the risk of tumor development in later lifestages. In fact, there is evidence to support the notion that susceptibility to tumor development from exposure to mutagenic chemicals during earlier lifestages is greater relative to exposure in later lifestages (U.S. EPA, 2005b). Depending on the goals stated in the problem formulation of a risk assessment (Chapter 3), consideration of studies that have examined cancer in adult humans and experimental animals following early-life exposure may be warranted.

4.2.2. Mode of Action Conceptualization

Dose-response characterization can proceed along two paths, one in which the quantitative dose-response values are developed with little or no insight into the MOA of an environmental toxicant, or one in which the dose-response values are informed by MOA. In the latter case, the assessment uses a broader body of scientific literature to look for commonalities in responses across studies, similarities to other chemicals, and mechanistic data from a wide array of studies and fields of specialization. MOA information is increasingly recognized in the scientific community as a foundation from which to build a dose-response characterization (Andersen et al., 2000; Andersen and Dennison, 2001; Clewell et al., 2002a; Preston, 2004). In order to conceptualize an MOA, the following are summarized: the available dose-response model(s), the mechanistic data that relate the critical effect(s) of interest to a particular dose metric, and the data supporting the choice of a likely or hypothesized dose metric. The following subsections describe topics to consider during the MOA conceptualization and example questions are addressed in Table 4-3.

4.2.2.1. *Summarizing the Available Dose-Response Data*

Quantitative assessments identify and summarize dose-response data to characterize the potential risks from exposure scenarios identified during the problem formulation (Chapter 3).

This process also interfaces with the exposure characterization (Section 4.3), where source-to-dose modeling informs assessors about the relevant exposure scenarios (i.e., route and duration) and likely ranges of external exposure levels for various lifestages. Because low-dose extrapolation has inherent uncertainties regarding MOA over dose ranges (Slikker et al., 2004a,b), the exposure characterization can help inform selection of the appropriate dose-response model from which to obtain a POD.

An exposure-response array can help identify critical outcomes (U.S. EPA, 2002a, Section 4.4.1) across dose ranges and aid in the conceptualization of the MOA. For instance, different effects at similar doses may originate through common mechanisms, and thus lend support to one or more MOAs. Alternatively, different effects across dose ranges may represent a gradient of effects operating through common mechanisms, and thus also lend support to one or more MOAs. It is also possible, of course, that different MOAs are operational across dose ranges, and an exposure-response array can be useful for defining the range of effects. Multiple responses can be described as a continuum of dose as well as continuum of lifestages when using this array. For instance, exposure-response arrays for various toxicity outcomes across developmental lifestages have been used to help inform outcome selection for dose-response. For example, exposure-response arrays have been used in the assessment of dibutyl phthalate (U.S. EPA, 2006a); where, using this approach, it becomes evident that adverse developmental effects occur at lower exposure levels than other adverse effects (e.g., hepatotoxicity). This approach is both important for dose-response characterization and is informative for risk characterization (Chapter 5). An alternative approach for summarizing the dose-response data is to use categorical regression (Section 4.2.3.1). This approach lumps different responses together by assigning key outcomes to severity categories–perhaps irrespective of MOA.

In circumstances where data exist for multiple lifestages, it is possible that effects at earlier lifestages pose greater risk due to the potential for irreversible changes (e.g., developmental neurotoxicity) or changes that confer an increase in risk to subsequent exposures in later lifestages. For instance, it is hypothesized that acute lymphocytic leukemia (the most prevalent childhood leukemia) results from an early (perhaps prenatal) initiation event forming a fusion gene, followed by a subsequent key event in later childhood (Greaves, 2003). If this initiation event could be ascribed to a particular environmental exposure, then this event could potentially be an important precursor event to consider due to the increased risk for latent

adverse effects, such as leukemia. Therefore, detailed MOA considerations can inform the selection of lifestage data for dose-response characterization. However, in cases where dose-response data do not exist for specific lifestages of concern (i.e., data gaps), MOA may be able to inform dose-response characterization for these lifestages by allowing for intraspecies (e.g., lifestage) extrapolation using biologically based modeling techniques (Section 4.2.3). Effects that are thought to share common key events in the proposed MOAs can give assessors confidence in choosing dose-response models that most closely relate to the underlying biology and adapt those models to other lifestages of interest.

4.2.2.2. *Mechanistic Data and Mode of Action*

The complexity of physiological development provides opportunity for toxic exposures to create TD effects that may or may not be relevant to all lifestages within a species. Developmental stages or age groupings (Table 3-1, U.S. EPA, 2005e) can be based on such metrics as growth rates/spurts, behavioral traits, organ systems, or perhaps functional development. It may be possible to plot these metrics for development throughout lifestages and across species. This comparison can aid in identification of organ systems (e.g., respiratory, cardiovascular, central and peripheral nervous systems, immune system) that might be at risk during comparable windows of exposure and can inform the decision of which effects and dose-response data are most useful. Although matching comparable lifestages across species is a challenge (U.S. EPA, 2002a, Table 3-1), such efforts have the potential to decrease the interspecies TD differences that influence dose-response relationships across species (Section 4.2.4.2).

4.2.2.3. *Selection of Dose Metric Informed by Mode of Action*

When physiologically based toxicokinetic (PBTK) models are available for a chemical, it may be possible to convert the external/applied dose in a study to an internal target tissue dose (i.e., dose metric). This can be an internal measure of the chemical or its metabolite(s) but can also be measures of adduct formations, cofactor depletion, etc. In addition to identifying the chemical moiety (e.g., adduct) of the dose metric, it is equally important to identify the most appropriate measure of the dose metric; frequently these are the average daily doses under the concentration versus time curve (area under the curve, AUC), peak concentration (C_{max}), or rate

of production. Selection of the appropriate dose metric for a given dose-response relationship is done in the context of what is known or hypothesized about the MOA, and thus is an inherently iterative process between dose-response characterization and hazard characterization (Section 4.1). In practical terms, the measured substance may not be the toxic moiety at the target tissue but rather a surrogate such as blood concentration of the parent compound or one or more of its metabolites. Another important consideration to the selection of the dose metric is the outcome. For example, peak concentration may be more important for some outcomes compared to others (e.g., neurotoxicity vs. tumors). When choosing among potential dose metrics, often the appropriate choice can be identified as the one that demonstrates a consistent relationship with positive and negative responses observed at various dose levels and across exposure scenarios within a single species (U.S. EPA, 2006b).

Clewell et al. (2002a) have proposed two criteria for dose metric determination: *plausibility*, defined as consistency with MOA and ability to simplify a complex dose-response relationship, and *conservatism*, defined as the selection of the dose metric that poses the highest risk or the lowest acceptable exposure level. It is the environmental exposure level to humans that is regulated as a result of risk assessment; thus, a potent dose metric is not synonymous with a potent external dose. Therefore, when there is insufficient data with which to determine the more appropriate dose metric, the one related to the most potent external exposure dose is often appropriate. More detailed information on dose metric selections is in *Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment* (U.S. EPA, 2006b).

Table 4-3. Examples of lifestage-specific questions for MOA conceptualization.

Topic	Lifestage-Specific Question(s)
Summarizing the Available Dose-Response Data (Section 4.2.2.1.)	What dose-response data/models are available for lifestages of interest (e.g., preconception, pregnancy, infancy, childhood)?
	Are the exposure scenarios in these studies the scenarios of interest? Can route and duration extrapolations be employed using modeling techniques (Section 4.2.4)?
	If data are available for a different lifestage than is of interest, are these amenable to extrapolation to lifestages for which there is little or no data (Section 4.2.4)?
	Can an exposure-response array inform the most relevant studies and outcomes?
Mechanistic Data and MOA (Section 4.2.2.2.)	Are TD effects known or hypothesized?
	What are the relative expression levels of the key players (e.g., receptors, metabolic enzymes, DNA repair enzymes) in the known or hypothesized MOA at the lifestages of interest?

	If multiple outcomes are evident, are they likely linked by MOA? Do the outcomes share common mechanisms? Or, do the outcomes represent a gradient of the same MOA?
Selection of Dose Metric Informed by MOA (Section 4.2.2.3)	What is the human lifestage exposure scenario of interest (route, duration, and pattern)? Are animal data available regarding the dose metric that is likely to be relevant to the human lifestage of interest? Is the selected type of dose metric appropriate for both the outcome and the exposure (e.g., duration) of interest? Are there models available which can convert the external/applied dose used in a study to an internal delivered dose (i.e., a dose metric)?

4.2.3. Analysis in the Range of Observation and Dose-Response Models

A number of models are typically employed in order to determine PODs, which are used for extrapolations in dose-response characterization and margin of exposure (MOE) analysis in risk characterization (Section 5.1.3). Data for dose-response characterization in the range of observation come in many forms: empirical PODs derived from either a NOAEL, a LOAEL, or sophisticated models incorporating mechanistic data. The nature and amount of data required for each type of dose-response characterization might represent a hierarchy, although the more sophisticated dose-response models still rely on the same experimental animal studies from which a NOAEL or LOAEL can be derived, either as a basis for curve fitting mathematical models or a starting point from which to calculate an internal target tissue dose using other modeling techniques.

In *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the EPA has adopted an approach that advocates the use of as much biologically informed dose-response data as possible, and suggests that "default" approaches be used only in instances where little data exists concerning an environmental toxicant of interest. PBTK modeling and BBDR modeling provide strong biological foundations for a chemical risk assessment; their application in risk assessment is discussed more thoroughly in *Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment* (U.S. EPA, 2006b). Moreover, their use in conjunction with statistical modeling is perhaps the most rigorous and scientifically based approach to dose-response modeling (U.S. EPA, 1999a).

The following brief descriptions summarize the types of analyses used in dose-response characterization. Example questions are addressed in Table 4-4, including those based on limited data sets and those requiring rich data sets for dose-response characterization.

Traditional approaches to dose-response modeling of a toxicant with an assumed nonlinear MOA have relied (and continue to rely) heavily on the use of empirical data points for determining PODs. Often these are NOAEL and LOAEL values derived from experimental dosing conditions in toxicologic studies. Two main disadvantages of using these single point estimate values are that they do not consider the shape of the dose-response curve, and they do not allow for estimation of risks at any exposure level of interest (Allen et al., 1998). Thus the use of NOAEL and LOAEL values alone represents the bottom tier of dose-response models and are used most often when limited data are available concerning the toxicant of interest.

Empirical modeling approaches, sometimes called curve fitting or statistical modeling, represent an improvement over traditional NOAEL and LOAEL dose-response characterization techniques. In these approaches, statistical models are fit to empirical response data (e.g., tumors) or precursor events (e.g., signal transduction or changes in blood hormone level). In some instances, low-dose extrapolation beyond the observed response data can be informed by precursor data over the low-dose range (U.S. EPA, 2005a). In other instances, linear low-dose extrapolation may be employed for extrapolating from the range of observation down to, for instance, background levels, rates, or incidence. This form of statistical modeling has been used for noncancer outcomes to develop quantitative risk estimates (discussed at the end of this section). The draft *Air Quality Criteria for Lead* (U.S. EPA, 2006c) contains further discussions on implications for low-dose extrapolation using statistical modeling (i.e., linear and log linear models).

Another form of statistical modeling for determining PODs is BMD analysis (Crump, 1984).[4] The BMD is defined as the dose at which a predetermined change in response incidence (e.g., 5% or 10% change in critical effect such as pup body weight or pup mortality) occurs; with the 95% lower confidence limit being the BMDL (Allen et al., 1994a,b; Faustman et al., 1994; Kavlock et al., 1995; Kimmel et al., 1995; U.S. EPA, 1995b). An advantage of this approach is that it attempts to fit statistical models to existing dose-response data, regardless of whether the MOA is linear or nonlinear, taking into account all of the data points in an individual dose-response study (Brown and Strickland, 2003). Thus, unlike the NOAEL/LOAEL approach, the BMD is influenced by the shape of the dose-response curve for developmental outcomes (Allen et al., 1998). The selection of BMD may require studies with more dose groups and a higher

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[4] EPA has developed software for BMD analysis, available at http://cfpub.epa.gov/ncea/cfm/bmds.cfm.

number of subjects, and therefore, can be performed only when the scientific database for an environmental chemical is relatively large. Because the BMDL depends on the study design, more rigorous studies generally have narrower confidence limits (Barnes et al., 1995). Importantly, the BMD approach is less sensitive to dose spacing, and thus a BMD can be determined in the absence of a NOAEL as well as for any increase in response level (Allen et al., 1998; Barnes et al., 1995). For further readings on choosing studies for BMD analysis, refer to the draft *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000d).

Categorical regression[5] analysis is similar to BMD analysis, but whereas BMD analysis uses a single study, categorical regression combines studies. In this method, data are pooled from different studies (possibly with different exposure parameters and outcomes) that are "assigned" to the same severity category (Brown and Strickland, 2003). An advantage to this approach is that a small number of studies can essentially be combined into one larger study and can thus narrow the confidence limits (Brown and Strickland, 2003). This methodology may be particularly useful in a lifestage approach where it is likely that fewer studies have been performed on the specific lifestages of interest or critical windows of susceptibility.

PBTK and BBDR modeling are perhaps the most amenable modeling techniques for using a lifestage approach as they are designed to mimic true biological processes and model whole organisms. Knowledge and understanding of TK differences during each lifestage (absorption, distribution, metabolism, and elimination), as well as anatomy and behaviors, are used in estimating delivered dose and may require modification of available adult models. Several reviews have described the variation in TK factors between adults and children (Besunder et al., 1988a,b; Bruckner, 2000; Clewell et al., 2002a,b, 2004; Hines and McCarver, 2002; McCarver and Hines, 2002).

Although the use of PBTK models for internal dose estimates is increasing, more effort is needed in developing such models for children's dosimetric adjustments across lifestages and experimental animal species. In this regard, pharmacokinetic data from pediatric pharmacologic studies could be appropriately applied for some portions of certain risk assessments for developmental lifestage environmental exposures. For instance, general knowledge of differences between adults and children in metabolic clearance of CYP3A-specific pharmaceutical substrates could be used by adjusting for these differences in activities in a TK

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[5] EPA has developed CatReg software, available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=18162.

model when the toxicant is thought to be metabolized by CYP3A (Ginsberg et al., 2004a,b). Ginsberg et al. (2002) compiled a database of 45 drugs for which TK data are available across lifestages.[6]

PBTK models are particularly useful for conducting extrapolations (e.g., route-to-route, duration, interspecies, including lifestage extrapolations). Other advantages are that these models can mimic any exposure scenario (continuous or otherwise) and changes in the underlying biology (e.g., development). For instance, if children are likely to be exposed to an environmental toxicant for one hour per day for five days a week (followed by 48 hours of no exposure), these models can predict the levels of metabolites of interest under these conditions. Similarly, numerous small exposure doses from breast milk to nursing infants could be modeled to determine steady-state levels of a toxicant at one month and at three months after birth. However, PBTK models are not necessarily applicable for extrapolating from short-term exposure studies to longer-term predictions. This is because the key events leading to the observed responses are not likely to be impervious to the effects of time and repeated exposure. Many dose-response relationships may be dependent on temporal changes in TD processes due to developmental- and exposure-induced changes (e.g., cell proliferation rates, DNA repair processes, receptor tolerance and desensitization, and age-related changes in physiologic parameters). Thus, it is feasible to predict steady-state levels of a compound in the body over long periods of time, yet the response to these levels may differ between short- and long-term durations of exposure. These differences due to duration of exposure highlight the importance of having dose-response data for the exposure duration and the lifestages of interest.

Application and review of PBTK models in risk assessment can be found in Ginsberg et al. (2004b), Pelekis et al. (2001), and U.S. EPA (2006b). There are some developmental lifestage PBTK models, some of which include infant exposure to chemicals such as dioxin in breast milk (Gentry et al., 2003; Lorber and Phillips, 2002), fetal exposure to ethylene glycol monomethyl ether (Gargas et al., 2000), and neonatal exposure to compounds such as lead (O'Flaherty, 1998) and perchlorate (Clewell et al., 2003; Clewell and Gearhart, 2002). Several pregnancy and lactation models have been reviewed (Corley et al., 2003).

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[6] This database can be accessed at http://www2.clarku.edu/faculty/dhattis.

BBDR models represent the state of the art in dose-response characterization, where mechanistic TD data are modeled in such a way that responses can be predicted, even at low exposure levels. Usually, output from a PBTK model serves as the dose input to a BBDR model, relating that dose to a response outcome (Andersen and Dennison, 2001; Ashani and Pistinner, 2004; Setzer et al., 2001). In addition to lifestage-specific TK data, the relationship between the internal dose metric and response may require lifestage-specific TD data. Currently, relatively few BBDR models are available due to the inherent complexity of integrating TK and TD data. Model transparency, quality criteria, and short shelf-life of some models beyond initial publication also limit BBDR model development (DeWoskin et al., 2001). The use of BBDR models is expected to increase as toxicologic studies move beyond more frank effects toward molecular precursor events (Andersen and Dennison, 2001; Faustman et al., 1999).

In instances where the dose metric of a toxicant of interest is structurally related to another compound for which there exists a validated BBDR model, consideration of the application of this model to the toxicant being assessed may be warranted.[7] As stated in *Evaluation of BBDR Modeling for Developmental Toxicity: A Workshop Report*, "the challenge is to define…application of a quantitative BBDR model…generalizable to other compounds in a similar class and perhaps to certain other classes of compounds" (Lau et al., 2000). For example, two chemicals might be hypothesized to affect similar TD processes (e.g., activation of a particular receptor), yet a BBDR model may exist for only one of the chemicals. If a PBTK model is available (or can be developed) for the chemical that does not have a corresponding BBDR model, it is conceivable that the existing BBDR model might be sufficient for analyzing both chemicals.

The top line in Figure 4-6 represents a BBDR model for the dose-response of chemical A, where TK_A, TD_A, and R_A represent the TK, TD, and response of interest related to chemical A, respectively. In this scenario, the TD of chemical B (TD_B) is thought to be equivalent to that of chemical A (i.e., both have the same MOA from a TD perspective). If a PBTK model (but not a BBDR model) exists for chemical B (TK_B), then the predicted internal target tissue dose of chemical B can be integrated into the existing BBDR model for chemical A.

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[7] Compounds with common TD effects may not necessarily be structurally related.

<div style="border:1px solid black; padding:1em;">

BBDR model exists for chemical A: $\{\mathbf{TK_A} \rightarrow [\mathbf{TD_A} = \mathbf{TD_B}] \rightarrow \mathbf{R_A}\}$

$\uparrow$

PBTK model exists for chemical B: $\qquad\qquad\qquad$ $[\mathbf{TK_B}]$

</div>
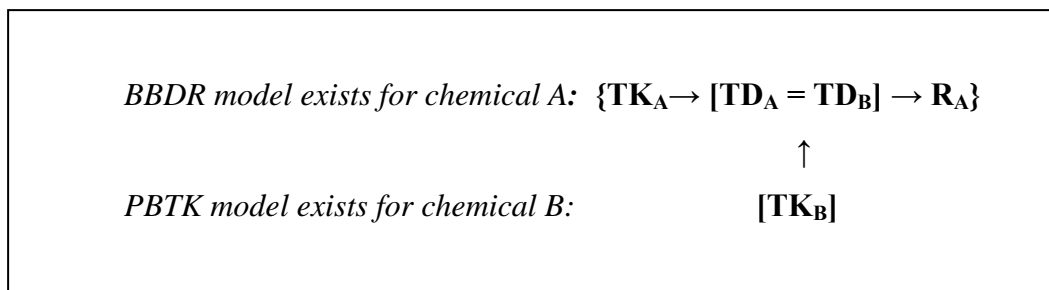
Figure 4-6. Use of BBDR modeling.

A probabilistic risk assessment approach has typically been used in exposure characterization and is increasingly being applied for dose-response characterization as data become available for physiological parameters such as genetic polymorphisms in TK and TD pathways (Beck et al., 2001; Pelekis et al., 2003). When readily measurable, inputs such as exposure dose and duration, intake rate, clearance, and body mass can be expressed as distributions and modeled in such a way as to estimate dose for a particular population, over a certain time frame, or at a specific location. Similarly, lifestage-specific parameters can be employed in order to estimate the variability in dose and response among lifestages (e.g., infants and children).

In regard to noncancer outcomes, one limitation applicable to many of the aforementioned dose-response modeling approaches is that the analyses are based on toxicologic outcomes as opposed to public health outcomes. QRE is a broad-based method for relating human exposures to non-toxicologic outcomes. For example, exposure to 1,2-dibromo-3-chloropropane can be linked to increases in infertility rates through mathematical modeling (Pease et al., 1991). In this regard, it is similar to BMD analysis, but whereas risk is typically defined by percent change (e.g., 1% or 5%) in a biological response (e.g., sperm count), QRE attempts to define risk (e.g., excess infertility cases) for all human exposure levels. The advantage of this approach over BMD is that a noncancer risk can be defined for any individual based on exposure level as is done for cancer assessments. Other examples of this type of analysis include associations among particulate matter and daily mortality and certain measures of morbidity (U.S. EPA, 2005d) and associations between acute ozone exposures and respiratory morbidity and mortality (U.S. EPA, 2005f). An inherent disadvantage to this approach is that acceptable levels of risk must be defined, whereas other approaches to noncancer dose-response modeling arguably rely less on value judgment.

Table 4-4. Examples of lifestage-specific questions for analysis in the range of observation.

Topic	Lifestage-Specific Question(s)
Selection of Dose-Response Models (Section 4.2.3)	What data were used to develop the dose-response curve? Are data available from the lifestage and exposure scenario of interest? Were there differences (e.g., in potency) in the dose-response curves for different lifestages?
	Was a model used to develop the dose-response curve and, if so, which one? What rationale supports this choice? For example, how was the benchmark response chosen?
	What modeling approaches are amenable to the available dose-response data? Is there sufficient data to support, for example, the use of biological modeling approaches?

4.2.4. Extrapolations and Risk Derivation from a Lifestage Approach

After PODs have been established from various dose-response studies or modeling techniques, low dose extrapolation is performed in order to derive dose-response values. Again, this may be done for assessments of narrow or broad scope (Section 3.1), and will have regulatory implications for various adjustments in order to extrapolate to the exposure scenarios and lifestages of interest. As described below, these adjustments may involve sophisticated approaches or default approaches that have developed over time. Despite the term *default*, many of these approaches are informed and supported by empirical evidence. For example, empirical analysis supports the use of body weight scaling (see below) to adjust for TK differences across species.

However, the use of more sophisticated techniques does not necessarily result in refinements of final reference or risk values. For instance, a recent assessment of xylenes resulted in nearly identical RfC values using either default approaches starting from a NOAEL or sophisticated PBTK modeling (U.S. EPA, 2003c). Despite the fact that this may be a possible outcome, the use of sophisticated techniques, MOA information, and lifestage analyses certainly improve the confidence that dose-response values (i.e., RfVs and risk values) are health protective. The following subsections describe topics to consider for extrapolations and risk derivation, and example questions are addressed in Table 4-5.

4.2.4.1. *Duration and Route Adjustments*

Experimental animal studies almost always employ discontinuous exposure protocols and therefore use continuous dose adjustment. Although such adjustments are conservative from a risk evaluation standpoint (i.e., they shift the dose-response curve leftward), mathematical adjustments do not necessarily maintain the dose-response relationship (i.e., AUC) that likely

reflects the MOA by which a response is generated. An alternative to continuous dose adjustment is to use PBTK models to determine (*in silico*) an applied dose (continuous or otherwise) that results in the same AUC or C_{max} which simulates that which could have been generated in the experimental animal under the original laboratory study conditions. This may require parameterization with lifestage- and species-specific data. Developmental windows of susceptibility are relatively short, thus the changing underlying biology during development suggests that C_{max} may be a more relevant dose metric in young children than AUC. Since the minimal exposure period to elicit an increased risk is often not known, especially during a window of vulnerability, the choice of exposure period is a critical decision point that integrates TK, TD, and exposure information.

For route-to-route extrapolation, default equivalent dose adjustments can be used. For example, standard mg/kg/day adjustments assume similar TK and TD processes between experimental animals and humans. However, such assumptions are tenuous because different cell types, enzymes, and proliferation rates exist across portals of entry. PBTK models can be used to predict target dose across routes by incorporating route-specific TK factors. A limitation, however, is that route extrapolations are not useful in instances where the critical effects are specific to the portal of entry. For more on route and duration adjustments, see *Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment* (U.S. EPA, 2006b) and *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002a).

4.2.4.2. *Interspecies and Intraspecies Adjustments*

The EPA RfC process describes the interspecies adjustment from experimental animals to human equivalent concentration (HEC) via dosimetric adjustment factors (DAFs) (U.S. EPA, 2002a). For oral exposures, default interspecies extrapolation based on body weight (BW) scaling, either BW^1 or $BW^{3/4}$, have been employed. In particular, $BW^{3/4}$ scaling is typically thought to account for TK differences among species, and therefore, often reduces the interspecies UF from 10 to 3 (U.S. EPA, 2002a). Recent harmonization efforts at EPA advocate the adoption of $BW^{3/4}$ scaling for RfD derivation in instances where there are limited data with which to perform an assessment (U.S. EPA, 2006d). This has been proposed in an effort to harmonize oral RfD methodology with RfC methodology. In addition, this effort also aims to

harmonize the use of $BW^{3/4}$ scaling in the application of DAFs for oral cancer assessments (U.S. EPA, 2006a).

For inhalation exposures, DAFs are applied on the basis of physicochemical, anatomical, and physiological parameters. These parameters include such factors as species-to-species ratios of surface area:ventilation rate, blood:gas partition coefficients, and regional deposition dose ratios for particulate matter. In the case of children, it is currently recommended that HECs and human equivalent doses (HEDs) be determined experimentally and theoretically (U.S. EPA, 2002a). In the absence of DAFs, simple ventilation rate adjustments can be made for HECs. Finally, it is worth noting that DAFs are thought to be most appropriately applied for chronic exposures, where the dose metric is likely best represented by AUC; discussion of adjustments for acute exposures can be found elsewhere (U.S. EPA, 2002a).

In addition to interspecies adjustments, $BW^{3/4}$ scaling may also be useful for intraspecies adjustments based on lifestage (U.S. EPA, 2006d). Pharmaceutical data indicate that TK processes (e.g., chemical half life) in children may also scale to $BW^{3/4}$, particularly in children over two months of age (Ginsberg et al., 2002, 2004a,b; Hattis et al., 2004). Under two months of age, however, the immaturity of such processes likely precludes scalability.

When more data are available for carrying out an assessment, lifestage considerations can be incorporated using either intraspecies adjustments or interspecies extrapolation (Figure 4-7). Adjustments across human lifestages from adult to earlier developmental stages includes exposure, TK, and TD considerations (Barton, 2005), and this process can be qualitative or quantitative (Ginsberg et al., 2002). Qualitatively, adult:child ratios for TK processes representing various metabolic pathways can be used to predict the relative difference in TK processes between children and adults for a toxicant that is metabolized by the same pathway. For example, the mean half-lives of several pharmaceuticals metabolized by CYP3A can be compared in adults and children; this ratio could then be used to adjust the intraspecies UF for an environmental toxicant that is known to be metabolized by CYP3A. Quantitatively, adult PBTK models (if available) could be parameterized in order to predict the dose metric in children. The left panel in Figure 4-7 depicts the frequent case where adult animal toxicity data is used to extrapolate to humans. If sufficient data and models are available, a subsequent intraspecies (or lifestage) extrapolation could be performed. The right panel depicts a less-frequent (but preferred) case where toxicity data in a lifestage of interest is used for interspecies extrapolation

to the corresponding lifestage of interest in humans. Importantly, this approach requires a qualitative or quantitative evaluation of how homologous the animal lifestage is relative to the lifestage of interest in humans. In the former case, such TK changes might increase the intraspecies UF with respect to TK consideration; it has been shown, for example, that such differences between adults and infants can exceed 3.2-fold (Hattis et al., 2004). In the latter case, the intraspecies UF may be reduced due to the improved characterization of TK. The advantage to this approach is that assessors may have greater confidence in extrapolating within the human species; on the other hand, this approach requires that the underlying toxic response and MOA are concordant across lifestages. This assumption may add additional uncertainty to the dose-response characterization.
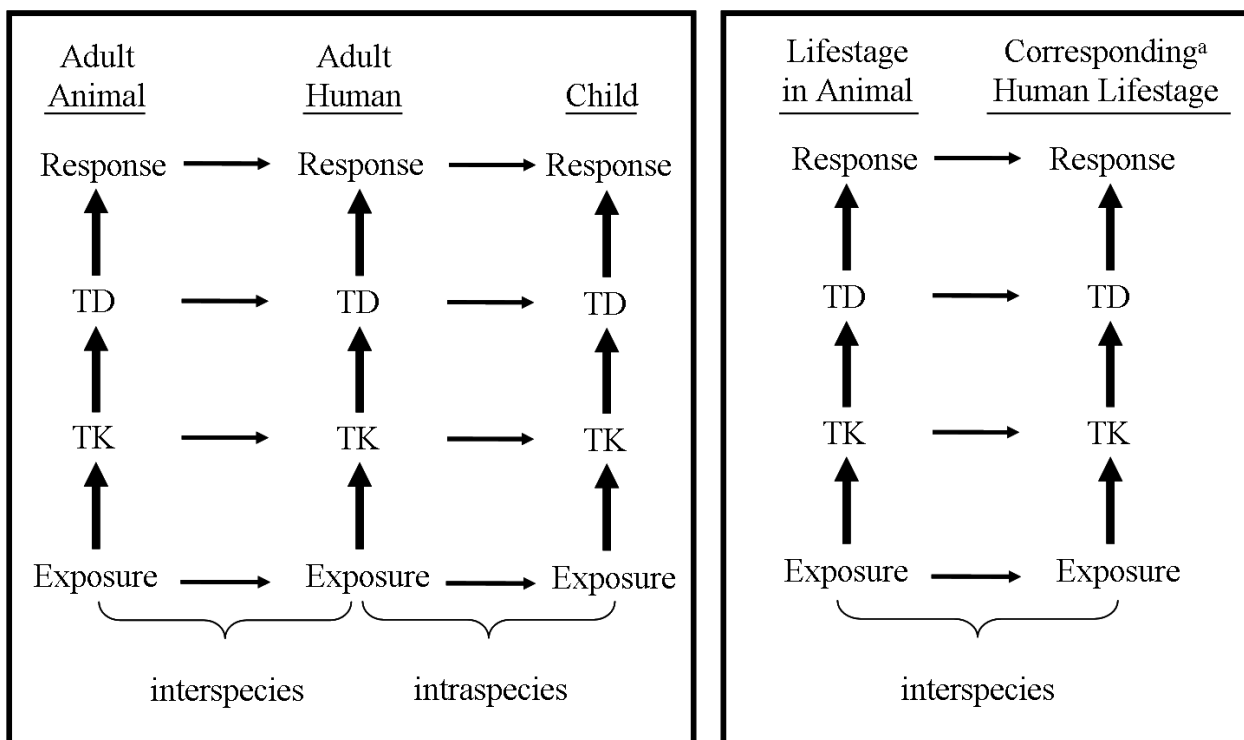
[a]Importantly, this approach requires a qualitative or quantitative evaluation of how homologous the animal lifestage is relative to the lifestage of interest in humans.

Figure 4-7. Interspecies and intraspecies adjustments with lifestage considerations.

More often, however, the data needed for lifestage extrapolation will be available only in experimental animals and thus will often require both qualitative and quantitative adjustments (Barton, 2005) (Figure 4-7, right panel). Qualitative adjustments include determining the

developmental stages in experimental animals and humans that exhibit the same window of susceptibility related to the critical outcome of interest. This may require both empirical evidence and expert judgment. Several articles have examined the relative development of organ systems across species (reviewed in Hurtt and Sandler, 2003a,b; Selevan et al., 2000; WHO, 2006). Quantitative adjustments are then needed to account for the TK differences that exist across species at the equivalent (with respect to the window of susceptibility) lifestages. For instance, rodents are born at an overall developmental stage roughly equivalent to the end of the second human trimester. Thus, if equivalent windows of susceptibility exist at these two different lifestages across species, then altogether different PBTK models and TK data would be needed to calculate the equivalent internal dose, i.e., a lactational model for the rodent and a pregnancy model for the human.

An advantage of this approach is that the assessor starts with age-relevant developmental effects (e.g., two-generation reproduction studies) as opposed to assuming concordance of effects across lifestages. This will likely have the effect of reducing the interspecies UF due to TK adjustments and due to a general increase in confidence that TD differences (if they exist) have been minimized. One caveat is that human data (from controlled exposures or epidemiologic studies) with which to test the predictive capability of the model is often nonexistent. Additionally, if extrapolation requires the use of different model structures (e.g., perinatal exposure in rats and fetal exposure in humans), then each model, with its own inherent uncertainties, may add to the overall uncertainty in the extrapolation (U.S. EPA, 2006b).

Because the majority of data concerning a chemical will pertain to nonhuman species, TK and TD data are important elements for lifestage-specific dose-response characterization. It is for this reason that PBTK and BBDR models have been emphasized for dose-response modeling under the lifestages approach. There are several examples where existing adult models have been adapted to developmental lifestages. Gentry et al. (2003) incorporated new tissue compartments and parameters into a previously published PBTK model for modeling isopropanol and acetone metabolism in adult humans and rats (Clewell et al., 2001). These additions include compartments for the uterus, mammary tissue, placenta, and fetus (Gentry et al., 2003), some of which are modeled to account for growth throughout gestation. Physiological parameter values were derived from numerous previous publications; currently, the EPA is developing relational databases for human and rodent physiological parameters so that these

values become more standardized and reduce some of the variability and uncertainty in PBTK models.[8] Pelekis et al. (2003) demonstrated the use of a lifestage approach by applying probabilistic analysis to a previously published PBTK model. Briefly, this study modeled daily exposure of individuals to dichloromethane from birth to 70 years of age using age-specific physiological parameters, partition coefficients, and CYP2E1 age-specific metabolic data. This model does not take into account age-related differences in exposure, nor are TD factors addressed (Figure 4-7, left panel). Lifestage data have also been used in BBDR modeling. For instance, a BBDR model has been developed for modeling the developmental effects on fetuses following maternal exposure to 5-fluorouracil on gestational day 14 resulting in birth defects and birth weight in rats (Figure 4-7, right panel) (Lau et al., 2000). This model employs a PBTK component that describes the formation of the metabolite, relates the metabolite levels to deoxyribonucleotide pool perturbation, and relates this perturbation to low fetal birth weight (Shuey et al., 1994) and fetal malformation (Lau et al., 2001; Setzer et al., 2001; Shuey et al., 1994).

4.2.4.3. *Low-Dose Extrapolation*

Ideally, extrapolation beyond the range of observation is informed by MOA. When MOA is not known, it is possible that the shape of the dose-response curve can be informative for low-dose extrapolation; however, Lutz et al. (2005) have demonstrated that these shapes can sometimes be misleading. For instance, the linearity of the dose-response curve often seen in epidemiologic studies may be due in part to interindividual genetic and life style differences as well as other issues related to epidemiologic studies such as difficulties in dose reconstruction. Conversely, Lutz et al. (2005) also demonstrated that animal bioassay studies that suggest a threshold effect may be misleading. For instance, *in silico* simulations of dose-response relationships can result in threshold (or J-shaped) relationships by chance; thus animal bioassays, often unrepeated, may suggest a relationship that does not exist in reality. Conolly et al. (2005), also using *in silico* methods, demonstrated that modeling of adaptive responses to DNA damage can result in both linear and threshold dose-response relationships depending upon model

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[8] Conversely, these databases can be used to incorporate variability in physiological parameters into probabilistic modeling techniques.

assumptions. Taken together, these studies highlight the importance of a strong understanding of MOA for choosing the most appropriate low-dose extrapolation approach.

The *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) advocate an MOA approach to low-dose extrapolation of cancer outcomes, where low-dose linear extrapolation is performed when a carcinogen is thought to act through a linear MOA (e.g., mutagenesis) or when the MOA for a carcinogen is not understood. This is based, in part, on the concept of additivity (Crump et al., 1976), where any amount of a carcinogen adds to the underlying biological processes that are responsible for the background incidence of a particular cancer.

Nonlinear extrapolation is used when the MOA can be demonstrated to result from a threshold (i.e., nonlinear) MOA and can be used for both cancer and noncancer outcomes. Although nonlinear extrapolation approaches are frequently used for noncancer outcomes, risk based approaches to noncancer outcome low-dose extrapolation, with potential relevance to cost-benefit analysis, have been proposed (Clewell and Crump, 2005; Gaylor and Kodell, 2002). There may also be biological support for low-dose linear extrapolation for certain noncancer outcomes. For example, 1,2-dibromo-3-chloropropane is thought to reduce sperm count by interaction with DNA (Pease et al., 1991); thus, like for mutagens, there may be a scientific rationale for using low-dose linear extrapolation for this compound.

4.2.4.4. *Reference and Risk Value Derivation*

Lifestage extrapolations for RfV and risk value derivations can affect the magnitude of the UFs applied in the final risk value derivation. Current practices for RfC and RfD derivation and the application of UFs are outlined in *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002a). New guidance on CSF derivation from early-life exposure to environmental agents can be found in the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). In brief, the new guidance states that for toxicants acting through a mutagenic MOA where data concerning early life susceptibility are lacking, early life susceptibility should be assumed and the following age-dependent adjustment factors (ADAFs) should be applied to the CSF:

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

No such adjustments are advocated for toxicants with either an unknown or non-mutagenic MOA. These adjustments are based, in part, on analyses indicating an increased incidence of tumor formation from early-life exposure as compared to adult exposure.

Historically, lifestage-related uncertainties have been folded into the database UF when the MOA is nonlinear. Lifestage-specific data gaps do not necessarily imply a greater database UF; rather, the method helps focus attention on the most critical data gaps deserving of additional uncertainty weighting. This additional weighting following uncertainty analysis (Section 4.2.7) would support prioritization of data needs. Indeed, the rationale for using the lifestage approach is to better characterize individual risk and thus decrease uncertainty in risk assessment.

Table 4-5. Examples of lifestage-specific questions for extrapolations and risk derivation.

Topic	Lifestage-Specific Question(s)
Duration and Route Adjustments (Section 4.2.4.1)	Do default duration adjustments maintain the relationship between exposure and response?
	Are the effects specific to the portal of entry?
	Can existing models be used to extrapolate to the lifestage-specific exposure scenario of interest using PBTK models?
Interspecies and Intraspecies Adjustments (Section 4.2.4.2)	Should the same interspecies factors (e.g., DAFs) be applied in deriving HECs and human equivalent doses for all lifestages?
	Can developmental lifestage dose-response characterization be conducted based on adult animal or human data (Figure 4-7)?
	Can developmental lifestage dose-response characterization be conducted based on developmental lifestage animal data (Figure 4-7)?
	What data are available to perform extrapolations for developmental lifestages?
Low-Dose Extrapolation (Section 4.2.4.3)	Is the MOA known?
	Is the chemical a known mutagen?
	Do statistical modeling approaches result in reasonable results in the low-dose range?
	Are PBTK models available? Can, for instance, a BMD_{10} be based on internal dose metric rather than applied dose?
Reference and Risk Value Derivation (Section 4.2.4.4)	Is the toxicant of interest mutagenic? If so, is there sufficient data to argue against using an ADAF?
	Have inter- and intra-species TK and TD differences been addressed through modeling?
	Are there significant concerns about a missing lifestage? What impact will this have on the database UF?

4.2.5. Variability Analysis

Variability analysis evaluates the range of values for a parameter in a population. This is particularly useful when sensitivity analysis has identified a key parameter as having a significant impact on model output. When an outcome is predicted to be sensitive to certain

parameters, probabilistic approaches (e.g., Monte Carlo simulation) can be incorporated into models (U.S. EPA, 2006b). This type of analysis, for instance, allows assessors to predict upper and lower bounds on a dose metric level in an experimental species; thus multiple calculations of the relevant exposure concentration for humans could be calculated and perhaps used for subsequent risk derivation.

Model evaluation may not be the final step in the dose-response process. Sensitive parameters provide red flags that are examined carefully for variability of these parameters within the population. Alternatively, the sensitivity might suggest the need for careful examination and consideration of susceptible lifestages. Example questions regarding dose-response variability are in Table 4-6.

4.2.6. Sensitivity Analysis

Sensitivity analysis allows risk assessors to examine which parameters in a model are most important to the outcome of concern. This analysis is a key evaluation technique for PBTK models. This analysis can identify the key parameters that can be further examined for accuracy, either through available data or estimation. In addition, selection of sensitive parameters could help in identifying more susceptible lifestages. For instance, model sensitivity to ventilation rate provides a starting point for addressing lifestage differences. Example questions regarding dose-response sensitivity are in Table 4-6.

4.2.7. Uncertainty Analysis

Uncertainty analysis can have both quantitative and qualitative components. Model uncertainty comprises that which is unknown about how well a model reflects the underlying biology. Models are approximations of biological processes, and therefore, have inherent shortfalls. Quantitative elements include model structure, choice of dose metric, and extrapolation procedures. Often these elements can be altered in order to compare model results. Results from this type of analysis, together with reasons supporting the various choices used in each model, can be expressed as subjective probabilities that each model is correct. Qualitative elements of uncertainty analysis include such things as choice of experimental animal species or the applicability of experimental animal species to the human lifestage of interest (Section 4.2.4.2). These particular efforts enhance the scientific underpinnings of the dose-response

characterization and are explicitly carried forward in the dose-response narrative (Section 4.2.9) through to the risk characterization (Chapter 5). See the final *Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment* (U.S. EPA, 2006b) for an in-depth treatment of PBTK model evaluation. Example questions regarding dose-response uncertainty are in Table 4-6.

Table 4-6. Examples of lifestage-specific questions for dose-response variability, sensitivity, and uncertainty analyses.

Topic	Lifestage-Specific Question(s)
Variability Analysis (Section 4.2.5)	How has variability been incorporated into a dose-response model? Have "average" individuals for one or more age groups been modeled, or has population variability (across age groups) been incorporated using probabilistic approaches?
	Are the differences in model outcomes among different age groups or the entire population greater or lesser than the typical intraspecies UF of 10?
Sensitivity Analysis (Section 4.2.6)	What lifestage-specific parameters (inputs) have been included in the dose-response model?
	What parameters have the greatest influence on the dose-response model outcome?
	Are the parameters to which a model is most sensitive likely to vary across lifestages? What is the likely impact of such differences on model predictions?
Uncertainty Analysis (Section 4.2.7)	Can the outcomes of multiple dose-response models and/or multiple variations (e.g., structures or curve fits) of such models be compared? How much do these outcomes differ?
	Can variability and uncertainty in a parameter be distinguished from one another? Is the variability true variation or is it a large component uncertainty that can be reduced through more lifestage-specific data collection or research?

4.2.8. Iteration with Hazard and Exposure Characterization

During the dose-response characterization, situations may arise where information obtained can lead to iteration with hazard characterization (Section 4.1). For instance, it is conceivable that evaluation of a PBTK model could lead to the conclusion that the model inadequately predicts empirical data. While this could be due to deficiencies in the model, it could also suggest that the dose metric previously hypothesized to be associated with a response may not be correct and thus may require a re-evaluation of the MOA. Such a situation may arise when the dose-response relationship between exposure and response does not become clearer when based on an internal dose metric.

Analysis of dose-response data could also warrant re-examination of the exposure characterization (Section 4.3). For example, data that indicate a sensitive dose-response relationship at environmentally relevant low-exposure levels, particularly in the context of precursor events, may suggest that certain exposure scenarios are more important than initially

thought and perhaps be an impetus for further characterization and refinement of exposure models employed for predicting external doses.

4.2.9. Lifestage-Specific Dose-Response Characterization Narrative

The dose-response narrative summarizes recommended estimates, data supporting those estimates, modeling approaches, a POD narrative, key default assumptions, uncertainty, sensitivity, and variability. The narrative also provides identification of susceptible lifestages and quantification of their susceptibility. A discussion of the strengths and limitations of the dose-response characterization are presented, highlighting significant issues in developing risk values, including alternative approaches considered equally plausible, and how these issues were resolved. Dose-response estimates may be accompanied by the descriptors used in the WOE evaluation (Section 4.1.3.1). For instance, a toxicant may be described as "likely to be carcinogenic to humans" when exposed by "oral route" (U.S. EPA, 2005a). In this regard, risk managers will be able to put each estimate into context. Questions to ask during the dose-response characterization narrative include the following:

- What were the results of variability, sensitivity, and uncertainty analyses?
- Are there data needs that should be highlighted to direct future research (by various scientific bodies and processes)?
- Are there lessons/implications for past, current, or future assessments?

4.3. LIFESTAGE-SPECIFIC EXPOSURE CHARACTERIZATION

4.3.1. Introduction

Exposure characterization is the analysis step in which human interaction with the environmental agent of concern is evaluated. Exposure (sometimes referred to as potential dose) is the pattern of contact of an individual with a toxic agent. To characterize exposure, an assessor needs information on the concentrations of a pollutant in exposure media, the activities that result in contact, and the transfer rates from the exposure media to the individual. Exposure results in an internal dose when the agent is transferred into and taken up by the body. Clearly, not all exposures will result in a significant dose (e.g., contaminated hands may be washed before dermal absorption or oral transfer can occur). Yet, it is the dose at the target tissue that will ultimately cause health effects. The primary purpose of a lifestage-specific exposure

characterization is to get a detailed description of the potential for exposure during preconception or developmental lifestages.

Exposure characterization (Figure 4-8) begins in the problem formulation phase (Chapter 3) with identification of potential sources, pathways, and scenarios. The resulting conceptual model (Section 3.2) is used to guide collection of available exposure data and other required information for exposure characterization. The assessor identifies and evaluates potentially significant exposure scenarios in order to conduct a lifestage-specific exposure characterization. Variability, sensitivity, and uncertainty analyses are conducted to determine impact of the available exposure data on the resulting analysis. The results of the exposure characterization are iterated with the hazard and dose-response characterizations if a critical window of susceptibility is identified that was not considered in the initial exposure characterization or if an important exposure period is identified that was not considered in the hazard or dose-response characterization. Finally, the assessor writes a summary of the exposure characterization, which includes a discussion of the confidence in the analysis results based on available data. This information feeds into the comprehensive lifestage-specific risk characterization (Chapter 5).

Throughout the exposure characterization, the assessor keeps in mind the relevance of the information to the overall goals of the assessment. It may be appropriate to refine the conceptual model (Section 3.2) or analysis plan (Section 3.3) after more thoroughly evaluating the available exposure data. For example, a conceptual model may focus on exposure to a chemical that is transformed in the environment before there is potential for a child to contact the agent. If the final form of the compound relevant for exposure was not considered in the conceptual model, then the conceptual model will need to be refined to consider all relevant agents.

4.3.2. Evaluation of Available Exposure Data

The objectives and scope of the risk assessment, defined in the problem formulation phase (Chapter 3), provide focus for identifying all the relevant human exposure data and other required information. To characterize exposure for a broad (e.g., national-scale) risk assessment will require distributional exposure factor data for all relevant lifestages. A narrow (e.g., site-specific) assessment will require measured or modeled environmental concentrations to estimate potentially significant exposures for all relevant lifestages.
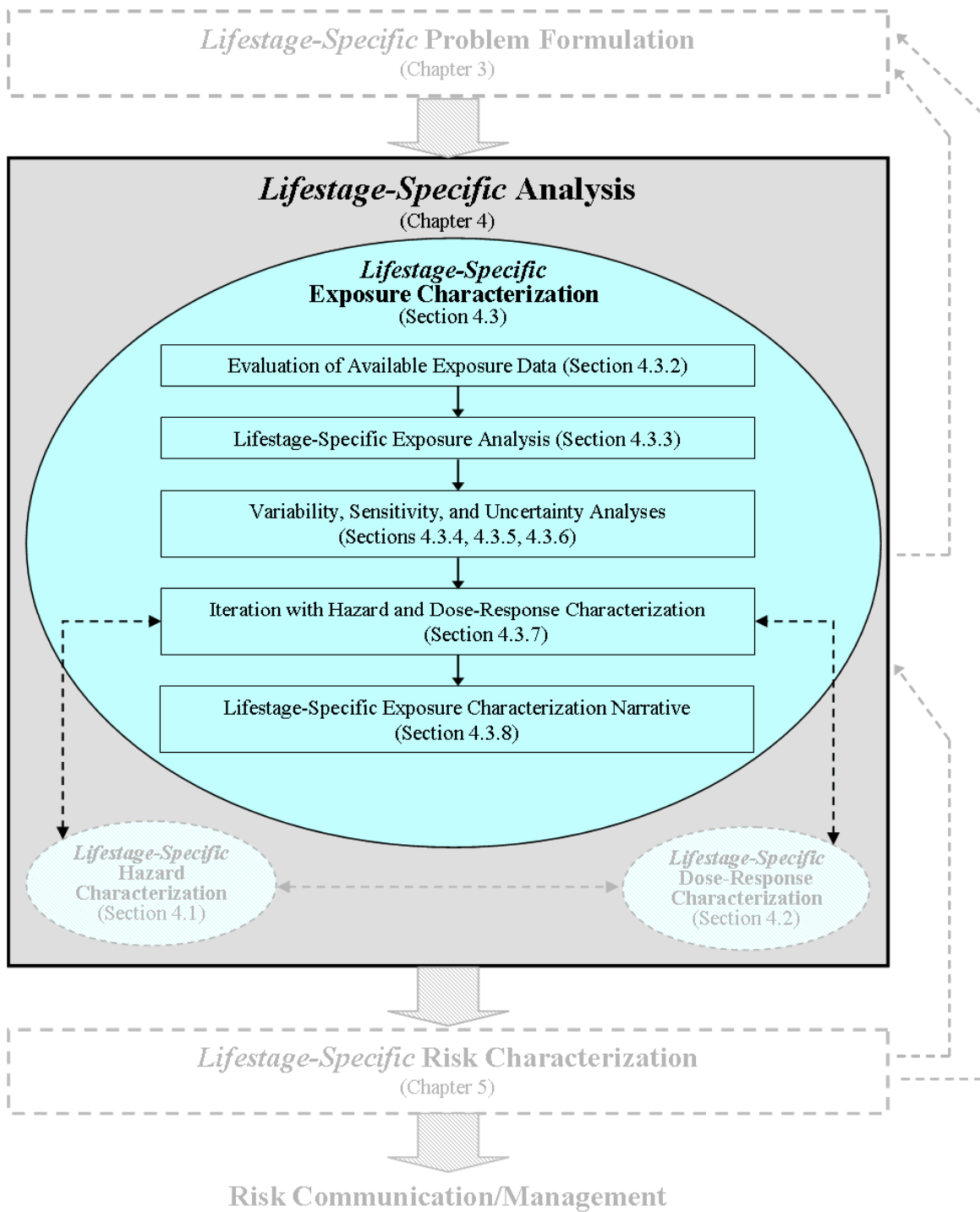
Figure 4-8. Flow diagram for lifestage-specific exposure characterization. Using the lifestage-specific exposure information identified in problem formulation (Chapter 3), exposure is estimated using a tiered approach. The lifestage-specific exposure is characterized by discussing the variability and uncertainty in the results. Key sources of variability and uncertainty can be assessed using sensitivity analysis. Iteration with hazard characterization (Section 4.1) and dose-response characterization (Section 4.2) (illustrated by dashed arrows) occurs throughout this process to ensure that critical windows of exposure are considered.

To focus on risk from exposure to children, the most appropriate data will be on sources and exposure media concentrations that have been identified in the locations where children spend time, which may change by developmental lifestage. For example, sources may be identified in

- residence and workplace for pregnant and lactating women;
- residence, daycare, and outdoor play areas for infants and toddlers;
- residence, school, and locations of after-school activities for school-age children; and
- residence, school, and locations of after-school activities and workplace for adolescents.

For a given source, exposure media (e.g., water, soil/dust/sediments, food, and objects/surfaces) and exposure routes (i.e., inhalation, ingestion, dermal absorption, and indirect ingestion) define the pathway of exposure (U.S. EPA, 2002c, 2003a). Figure 4-9 highlights the stages of development and their relevant exposure routes. The result of evaluating the exposure data would be a table in which potential exposure routes are identified for each exposure medium (direct and indirect) (Hubal et al., 2000).

Exposure media may also change with lifestage. For example, the fetus will be exposed to cord blood and amniotic fluid, the infant to breast milk, the teething child to many objects for mouthing, the school-age child to pesticides used in the classroom, and the adolescent to vocational or recreational hazards.

For any given pathway, a set of associated exposure scenarios describes how an exposure takes place and is used to estimate distribution of exposure. An exposure scenario is defined by the combination of all the discussed details (Hubal et al., 2000). Example questions for refining life-stage specific scenarios to facilitate exposure analysis are presented in Table 4-7.

Children may experience unique exposure patterns that are important to consider in relation to their kinetic development and critical windows for effects. Therefore, the assessor must carefully consider the temporal scale for estimating exposures and doses in children. Exposure estimates may be presented as

- peak doses
- exposures occurring over a very short period of time (e.g., minutes)
- time weighted averages (e.g., TWA over 8 hours)
- single day doses (representing the sum over 24 hours)
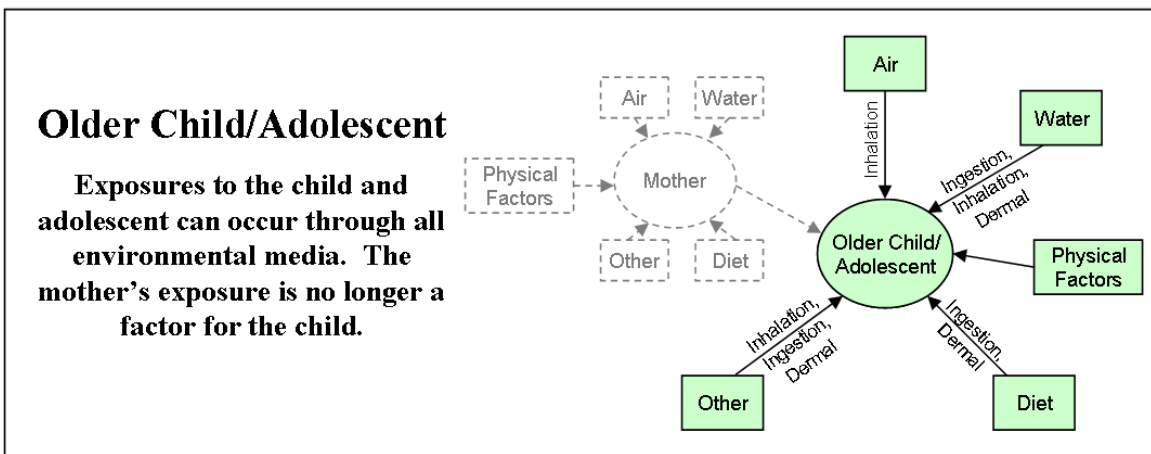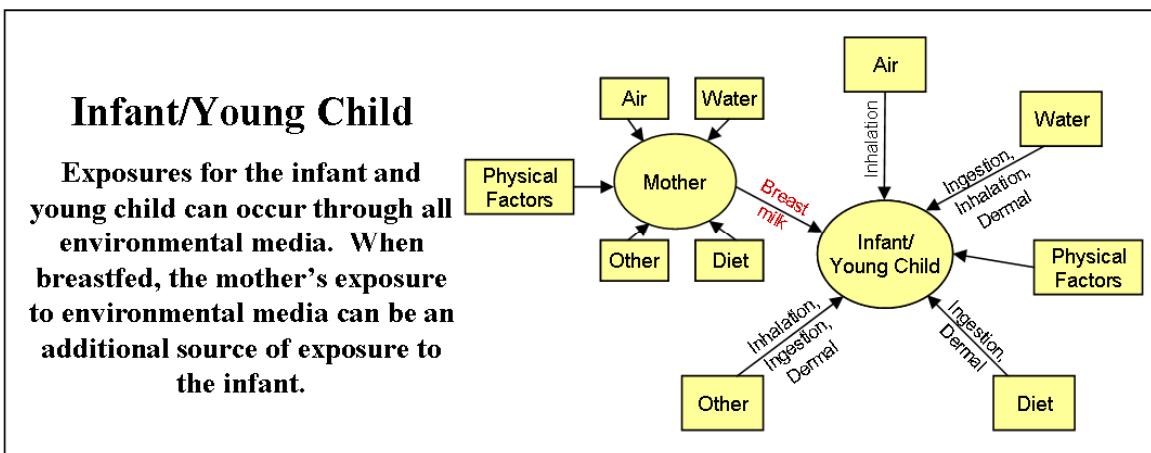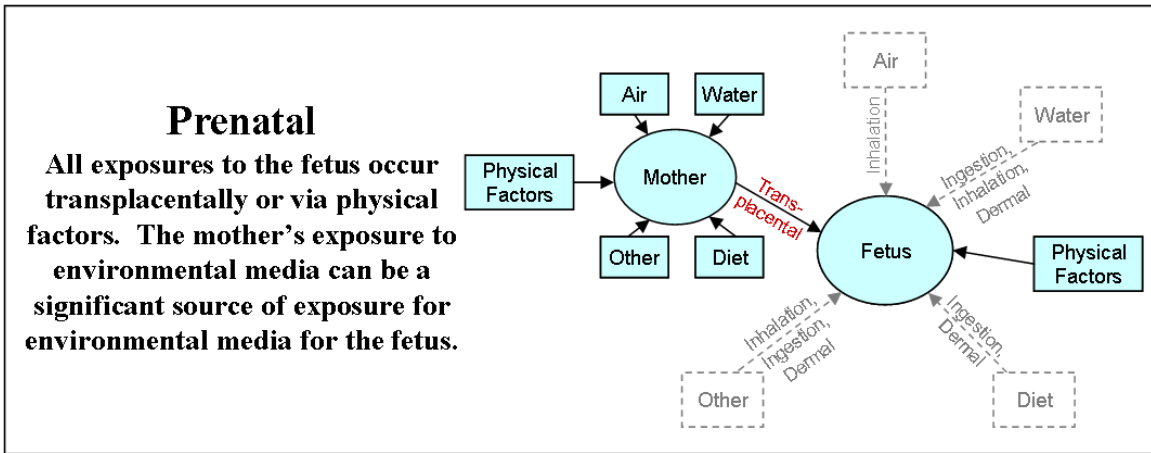
Figure 4-9. Exposure routes during developmental lifestages. The solid lines represent relevant exposure, while dotted lines represent exposures that are not relevant to the specific lifestage. During gestation, the majority of exposures (except for physical factors) occur transplacentally through exposure to the mother. After birth, exposures may either be directly to the child, with an additional route from the mother for those agents that may be present in human milk.

Table 4-7. Examples of lifestage-specific questions for scenario development.

Sources of Exposure	What are the sources of exposure to chemicals or agents that are of special concern for children?
	Where in the environment can the child come into contact with the chemical? In what quantities? If it is a consumer product, how is it used by children?
Pathways of Exposure	What are all the potential exposure media (e.g., breast milk)?
	What are all the potential exposure routes (hand-to-mouth ingestion)?
	What are the specific pathways that may be of concern for children (e.g., absorption from amniotic fluid, ingesting breast milk, ingestion of food eaten off contaminated floor)?
	How are parents and/or children being exposed, from the source to the absorbed dose, for all pathways of exposure?
Lifestages of Exposure	What are the potentially exposed lifestages?
	Are there any community factors that may put a subgroup of children at higher risk (e.g., ethnic, cultural, racial, or socioeconomic groups)?
	Are there any individual characteristics that may put an individual child at higher risk (e.g., health status, nutritional status, genetic susceptibility)?
Exposure Patterns	What is the relevant time frame of exposure (e.g., acute, short term, chronic, intermittent)?
Locations of Exposure	What are the potential locations of exposure (e.g., in utero, residence, school, outdoors, indoors)?
	Are there other relevant factors that may be relevant for identifying exposure scenarios for specific lifestages? Geographical location? Urban, rural? Near water bodies? Near parks? Near industrial sites?
Activities and Behaviors	What are the potential activities (e.g., mouthing, playing soccer, mowing lawns) at the lifestages of concern that may lead to exposure?
	What developmental stage-specific behaviors may lead to contact with the chemicals? How do the behaviors vary among children of various ages?

- short-term average daily doses (e.g., averaged over a month or a year)
- lifetime average daily doses

A potential problem with the time integration of exposure estimates is that the pattern of exposure can be obscured. If the exposure pattern is relatively continuous and at a constant level, the time averaged doses will be close in magnitude to single-day dose estimates and will match actual human experience. However, when infrequent exposure events of high magnitude and short duration are averaged, they are equated with continuous, lower-level exposures that do not match human experience.

The following subsections describe information required to characterize exposure. Data and other information used to assess exposure include chemical properties, environmental sources, fate and transport (Section 4.3.2.1), environmental media concentrations (Section 4.3.2.2), lifestage-specific exposure measurement data (Section 4.3.2.3), lifestage-specific exposure factors (Section 4.3.2.4), and cumulative evaluation of environmental stressors (Section 4.3.2.5). Although there have been several large human exposure studies conducted to collect

integrated data on environmental concentrations, personal exposure measurements, and time-activity data (e.g., *Human Exposure Measurements: National Human Exposure Assessment Survey* [NHEXAS][9]), these studies have focused on the adult lifestage. As such, these data may be useful for characterizing preconception exposures to the parent but less so for accurately characterizing exposures to pregnant women and to very young children. Nevertheless, these provide a significant data source that should be evaluated with respect to the utility for addressing the significant life-stage exposures of a given assessment. The Human Exposure Database System (HEDS)[10] is an integrated database system that contains information related to many of these EPA human exposure research studies. Some additional life-stage specific resources are described in the following subsections and example questions for each section are presented in Table 4-8.

4.3.2.1. *Chemical Properties, Environmental Sources, Fate, and Transport*

An agent of concern may be released into the ambient environment from multiple sources (e.g., industrial, agricultural, mobile, household, and natural sources). Also, the agent of concern may be released directly into exposure media (e.g., via occupational activities, residential use of consumer products, and cooking activities) of direct concern for a lifestage-specific assessment.

Once a chemical is released into the environment, it may be chemically modified or transported, in its original or transformed state, into an exposure medium of concern for children (e.g., outdoor air, residential water, food, and/or breast milk). Scientists and engineers can predict the environmental movement of a chemical using information on chemical properties (e.g., volatilization rate, water solubility, soil/water partitioning coefficients, chemical state, and bioavailability) and environmental conditions (e.g., soil characteristics, amount of rainfall, wind direction, and presence of water bodies). Information on the form, fate and transport of the agents in the residential environment is also required for exposure characterization and can be predicted based on properties of the chemicals and residential environment (e.g., size of rooms, surface types, air exchange).

Information on these types of releases and associated fate and transport may be generally required for risk assessment and is not lifestage specific. However, information on chemical

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[9] The NHEXAS database is available online at http://www.epa.gov/heasd/edrb/nhexas.htm.
[10] The HEDS database is available online at http://www.epa.gov/heds.

properties is required to identify potential lifestage concerns as well as particular scenarios and pathways that may be of particular concern for children. For example, if a chemical is lipid soluble, an infant's ingestion of breast milk may be an important route of exposure to consider. As another example, if a chemical is highly volatile, the inhalation pathway will be of particular concern because on a body-mass basis, young children have higher ventilation rates than adults.

4.3.2.2. *Environmental Media Concentrations*

Exposure characterization requires information on contaminant concentrations in the exposure media in the environment where the individual spends time. Contaminant concentrations can be measured directly in the exposure medium of interest or predicted by using information on the release of the contaminant and subsequent fate and transport in the environment. Site-specific assessments will require measured and/or model information on concentrations of an agent in the relevant media (e.g., soil, water, indoor air). For broad (e.g., population-based) assessments, information may be available in the literature.

The largest exposure study conducted to collect exposure media concentration data for children is A Pilot Study of Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (CTEPP) (Morgan et al., 2006). In this study, concentrations of a wide range of environmental contaminants were measured in multiple media in the homes and daycares of children from ages 3 to 5 years. Exposure media concentration data was also collected for children in the Minnesota NHEXAS study (Adgate et al., 2004). Recently there has also been considerable research conducted to develop residential models for several environmental contaminants including pesticides (Stout and Mason, 2003) and pthalates (Xu and Little, 2006). These models use data collected in controlled laboratory settings and test house situations and may provide insight into potential pathways for lifestage-specific exposures.

4.3.2.3. *Lifestage-Specific Exposure Measurement Data*

Additional data may also be available that provide a more direct measure of exposure. Personal monitoring techniques, such as the collection of personal air or duplicate diet samples, are used to directly measure exposure to an individual during particular time intervals. In children especially, different factors might affect the child's dose. It is important to give consideration to measurement techniques at the physical locations where the child spends his/her

time (e.g., home, school, daycare) as well as the child's characteristics and behaviors. For example, the breathing zone of a child is closer to the floor than the breathing zone of an adult, and concentrations of chemicals that are heavier than air may be higher in areas closer to the ground. Some of these types of data are available in the CTEPP study (Morgan et al., 2006) and in other smaller studies that have been published in the literature (Adgate et al., 2004; Cohen Hubal et al., 2006; Liu et al., 2003; MacIntosh et al., 2001).

For some environmental contaminants, biomarkers can serve as a useful measure of direct exposure aggregated over all sources and pathways. However, few studies using biomarkers have collected all the information required to accurately estimate exposure. The most significant source of biomonitoring information is the *Third National Report on Human Exposure to Environmental Chemicals* (CDC, 2005), collected as part of the National Health and Nutrition Examination Survey (NHANES) study.[11] This study measured a wide range of chemicals in the blood and urine of a representative sample of the U.S. population. However, young children (under 6 years) are only monitored for a select group of chemicals in this study (lead, mercury, pthalates, and organophosphates). Other lifestage-specific biomonitoring data have been collected in studies conducted by the National Institute of Environmental Health Sciences (NIEHS)/EPA Centers for Children's Environmental Health and Disease Prevention Research (Kimmel et al., 2005). Several of these centers have collected data from a variety of biological media from both pregnant mothers and their infants. Additional information on collection and interpretation of biomonitoring data for lifestage-specific exposure characterization is presented by Barr et al. (2005).

It is important to note that biomonitoring data may demonstrate exposure, although it may be difficult to translate into estimates of exposure. Biomonitoring may be useful for quantifying exposures at the population level, if the relationship between the substance found in the body and the amount of substance the child was in contact with can be established. Currently, there are significant research efforts associated with interpreting biomonitoring data for assessing human exposure to environmental agents (Albertini et al., 2006; NRC, 2006).

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[11] Details on the NHANES study are available online at http://www.cdc.gov/nchs/nhanes.htm.

4.3.2.4. *Lifestage-Specific Exposure Factors*

In addition to information on sources, exposure media concentrations, and human exposure measurements, exposure factor data (time-activity data; product use; and air, fluid, and dietary intake rates) are required to characterize exposure. Information is required on activities and behaviors that result in significant exposures (e.g., breast feeding, mouthing, sports, after-school employment) for each lifestage. The most current version of *Child-Specific Exposure Factors Handbook* (U.S. EPA, 2002c) could be the starting point for identifying these values. The purposes of the *Child-Specific Exposure Factors Handbook* are to summarize key data on human behaviors and characteristics that affect children's exposure to environmental contaminants and to recommend values to use for these factors. Data contained in the handbook includes drinking water consumption; soil ingestion; inhalation rates; dermal factors including skin surface area and soil adherence factors; consumption of produce, fish, meats, dairy products, homegrown foods, and breast milk; activity patterns; body weight; and consumer products. Age-specific activity data are also available from the *Consolidated Human Activity Database* (CHAD).[12]

Within each lifestage there may be a series of critical developmental periods for which exposure could be characterized. These periods may be defined on the basis of exposures that can affect development (e.g., parental preconception exposures, U.S. EPA, 1991, 1996), or windows of potentially high exposure due to age-specific behaviors (e.g., crawling, teething), activities (e.g., types of sport/other activities, length of sport seasons, physical education requirements), and physiology. Behavior varies by developmental stage, and this may have a significant impact on exposure.

EPA has recommended a standard set of age groups (Table 3-1) for exposure assessors to consider when assessing childhood exposure and potential dose to environmental contaminants and for purposes of designing exposure monitoring studies (U.S. EPA, 2005e). These age groups reflect a consideration of developmental changes in various behavioral, anatomical, and physiologic characteristics that impact exposure and potential dose. Data from the *Child-Specific Exposure Factors Handbook* emphasize the value of independently assessing the relevant age group where sufficient data are available. In the case of vegetable intake, data indicate that biases are introduced when combining age groups, especially for the <1-year-olds

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[12] The CHAD database is available online at http://www.epa.gov/chadnet1/.

because children 6 to <12 months eat three times as many vegetables than children 3 to <6 months old.

Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants (U.S EPA, 2005e) also recognizes that exposure factors data may not be available for many of the recommended age groupings or that a specific age group may not need to be the subject of a particular assessment; therefore, flexibility and professional judgment is essential in applying these generic age groupings. There may be instances where combining some of these age groups (e.g., combining the first three groups into one representing birth to < 6 months) could be considered when estimating exposure or potential dose, especially if little variation is expected. For example, there is little variation in ventilation rates for children between 11 and 18 years. Therefore, these age categories can be combined into one age group representing 11 to <18 years. In addition, there may be instances where it is not necessary to address every age group in Table 3-1 because the focus of a risk assessment may be on toxicity data that indicate a health effect for which only one or two of the age groups represent a critical window.

Exposure factors and resulting effects during developmental stages may be a function of additional individual and population characteristics. These factors may be characteristics of the communities in which children live and include, for example, SES, family size, ethnicity, cultural setting, geographical location, and seasonal considerations (e.g., temperature, humidity, rainfall, sun exposure). Other factors specific to the individual child include genetic susceptibility, nutritional status, and health status. Mechanisms of vulnerabilities associated with individual and community characteristics include differences in susceptibility, differential exposure, differential preparedness, and differential ability to recover. These mechanisms are defined and discussed in the Framework for Cumulative Risk Assessment (U.S. EPA, 2003a, pp. 39–42). Discussion on other risk factors, effect modifiers, and confounders is detailed in Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991, Section 3.1.2.1.1.c, pp. 24–25) and Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996, Section 3.3.1.5.3, pp. 60–61).

4.3.2.5. *Cumulative Evaluation of Environmental Stressors*

The focus of this section is the examination of vulnerability associated with differential exposure due to lifestage. It is difficult to separate consideration of vulnerability due to lifestage from consideration of vulnerability due to other key individual (e.g., ethnicity, dietary preferences) and community characteristics (e.g., social and physical home environment, religious/cultural practices) that may influence or modify exposures. In order to fully characterize risk to children, consideration could include environmental heath disparities (e.g., residential segregation) (Gee and Payne-Sturges, 2004) and the built environment (e.g., design and integrity of housing, land use and planning) (Cummins and Jackson, 2001).

EPA is examining the full range of issues related to characterizing risks to children through a variety of initiatives, including development of *Framework for Cumulative Risk Assessment* (U.S. EPA, 2003a). As EPA develops further guidance for cumulative risk assessment, the full range of vulnerabilities will be considered more consistently in both hazard characterization (Section 4.1) and exposure characterization. A child-centered approach (Section 3.2.3) to cumulative risk assessment may be useful in moving these issues forward (WHO, 2006, Chapter 5).

Table 4-8. Examples of lifestage-specific questions for evaluation of the available exposure data.

Topic	Lifestage-Specific Question(s)
Chemical Properties, Environmental Sources, Fate, and Transport (Section 4.3.2.1)	What are the physical and chemical properties of the chemicals or agents? What is known about their fate and transport?
	What are the environmental conditions (e.g., wind direction, rainfall) that may affect the fate and transport of the chemical(s)? In the case of a release of an air pollutant, are there areas highly populated by children that are downwind from the release (e.g., schools, play grounds)?
	What are potential chemical sources (industrial, agricultural, occupational, residential, consumer product) of the compound?
	What are the release rates from the chemical source? What is known about the manufacturing processes that may lead to information about where the chemical can be found (e.g., children's toys, play ground equipment, certain foods)?
	Are there data on the temporal and spatial patterns of compound release and transport relevant for specific lifestages? Is the release from the source continuous, periodic, or intermittent?
	What does the fate of the compound imply for exposure? Is the exposure to the released compound a byproduct created in the manufacturing process or a degradation product? If not, what are the compounds that should be assessed?
Environmental Media Concentrations	What are the concentrations of the chemicals in various media (e.g., air, water, food, breast milk, on surfaces, in consumer products) that the child may come into contact with during an exposure?

(Section 4.3.2.2)	Are the ranges and distributions of environmental media concentration data relevant for children's exposure?
	What bioavailability data are there for the chemical(s) from the various exposure media?
	How are the concentrations in environmental media changing over time? Are these intermittent?
	If environmental monitoring data are not available, are there models that can be used to predict the concentration at the exposure point?
Lifestage-Specific Exposure Measurement Data (Section 4.3.2.3)	Are relevant exposure measurements available for various lifestages (parents, infants, and children)? Are these direct or indirect measurements of exposure (e.g., personal air, handwipes, duplicate diet, biomarkers of exposure)?
	Are there biomonitoring data that demonstrate exposure potential? Is additional information available to use the biomonitoring data to estimate a population's exposure?
	Are there lifestage-specific data in biological media (e.g., maternal cord blood, placenta, meconium)? Can these be used to estimate exposure or to indicate potentially critical windows of exposure?
Lifestage-Specific Exposure Factors (Section 4.3.2.4)	What are the child-specific exposure factors (U.S. EPA, 2002c) that characterize the exposure scenarios?
	What are the ranges or distributions of exposure factors for relevant lifestages?
	Are time-activity data available for all relevant lifestages?
	Are dietary data available for all relevant lifestages? How do differences in diet during specific lifestages impact exposure?
	Are product-use data available for all relevant lifestages (e.g., pregnant women, children)? Are the products used by children or in proximity of children?
	Are data available for other children's exposure factors (e.g., contact rates for the individual with exposure media, contaminant transfer efficiency from the contaminated medium to the individual)?
	Do children's physiological parameters influence exposure to the specific agent (e.g., body weight, uptake rates – inhalation, dermal absorption, gastrointestinal absorption)? If so, are there data available (Hattis, 2004)?
Cumulative Evaluation of Environmental Stressors (Section 4.3.2.5)	Are there data indicating potentially important co-exposures with chemicals that may interact to increase health risk for a sensitive lifestage?
	Are there data on relevant non-chemical stressors that may impact exposure and/or increase vulnerability of specific lifestages (e.g. SES, health status)? Are there any community factors that may put a subgroup of children at higher risk (e.g., ethnic, cultural, racial, or socioeconomic groups)?
	Are there any individual characteristics that may put an individual child at higher risk (e.g., health status, nutritional status, genetic susceptibility)?

4.3.3. Lifestage-Specific Exposure Analysis

Based on the data and information identified for exposure characterization (Section 4.3.2), the scenarios developed during problem formulation (Chapter 3) could be refined to facilitate exposure analysis. Exposure estimates may be developed for all relevant lifestage-specific scenarios. At this point in the assessment, patterns of exposure will be characterized (intermittent, continuous, acute, or chronic) and exposure levels will be quantified. Because children may have higher exposures (Section 4.3.2.4) or because they may experience unique

exposure patterns (Section 4.3.2.5), exposures may be significant during critical windows, which can then affect the outcomes observed.

The health effect of concern is considered when selecting the appropriate temporal scale for estimating exposure/dose. Depending upon the problem, it may be important to consider peak exposures as well as exposures that have been averaged over a specified period of time (U.S. EPA, 2005e). Assessments of agents with multiple sources or in multiple media may require additional analysis to estimate children's exposure patterns. This would indicate that even for a screening-level analysis (Section 4.3.3.2.1), a large number of factors may need to be collected and tracked, along with their associated variabilities and uncertainties. Thus to efficiently and effectively assess children's exposures, a person/population-oriented approach (Section 3.2.1) may be needed for all but the most basic assessments.

To conduct the lifestage-specific exposure characterization, a calculation approach described in Section 4.3.3.1 is selected on the basis of available data and the risk assessment questions that were defined during the problem formulation phase (Chapter 3). Typically, an exposure characterization will begin with a screening-level assessment (Section 4.3.3.2.1) and then, if there appear to be significant exposures or an unacceptable level of uncertainty, a second, more refined level of analysis will be conducted (Section 4.3.3.2.2). This type of tiered level analysis is often used to facilitate efficient allocation of resources. Often, two or more calculation approaches will be used and the results compared in the exposure characterization narrative (Section 4.3.8). The following subsections describe each tier, and example questions are presented in Table 4-9.

4.3.3.1. *Exposure Measurement and Estimation Approach*

Three approaches may be used to calculate exposures: (1) the point-of-contact approach, (2) the scenario evaluation approach, and (3) the dose reconstruction approach. Each approach has advantages and disadvantages over another.

The point-of-contact approach, sometimes referred to as the direct approach, involves measurements of chemical concentrations at the point where exposure occurs (at the interface between the person and the environment) and records of the length of contact with each chemical. This approach does not take into account an individual's characteristics or behaviors.

The scenario evaluation approach, sometimes referred to as the indirect approach, utilizes data on chemical concentration, frequency, and duration of exposure as well as information on the exposed lifestage. Child-specific behaviors and physiologic characteristics may be assumed on the basis of exposure factor data (U.S. EPA, 2002c) or from exposure study databases (the *Consolidated Human Activity Database* [CHAD]; the *Human Exposure Database System* [HEDS]),[13] or they can be obtained specifically for the assessment (e.g., by questionnaire, diary, videotaping). Chemical concentration may be determined by sampling and analysis or by use of fate and transport models (including simple dilution models). Models can be particularly helpful when resources for additional sampling are limited but some analytical data are available.

Finally, the dose reconstruction approach allows exposure to be estimated from dose, which can be reconstructed through internal indicators (e.g., biomarkers, body burden, excretion levels) after the exposure has taken place. The use of biomarkers of exposure or effect may provide a more detailed analysis; however, only a few examples currently exist for applying this approach successfully. At the present time, much of biomarker data are difficult to interpret, either because the presence of a biomarker may not be unique (e.g., many stressors result in a change in the same biomarker) or there may not be adequate exposure pathway information to link the biomarker to the exposure. Currently, this approach is most successful for persistent compounds.

4.3.3.2. *Analysis Level or Tiered Assessment*

Typically, an exposure characterization will begin with a screening-level assessment and then, if there appears to be significant exposures or an unacceptable level of uncertainty, a second, more refined level of analysis will be conducted. Probabilistic techniques may be used at either level of analysis depending on the types of scenarios being evaluated. The major difference between the levels of assessment described below is related to the assumptions that are used.

The first tier screening assessment (Section 4.3.3.2.1) is used to identify and prioritize potentially important exposures. After results of the screening assessment are compared with results of the hazard characterization (Section 4.1), a more refined assessment (Section 4.3.3.2.2)

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[13] The CHAD database is available online at http://www.epa.gov/chadnet1; the HEDS database is available online at http://www.epa.gov/heds.

may be required, using more realistic estimates of exposure for selected scenarios to reduce the uncertainty. This second tier is generally more resource-intensive than the first tier and is used to refine estimates for exposure scenarios that were identified as potentially significant in the screening assessment. Finally, if a high level of uncertainty remains around estimates of exposure following a refined assessment, supplemental data collection may be needed.

4.3.3.2.1. *Screening assessment.* The purpose of a screening tier is to identify probable pathways and scenarios and to rule out insignificant ones. Bounding values for exposure factors and conservative simplifying assumptions are used at this level of analysis. As a result, the output may have a high level of uncertainty. Historically, deterministic calculations were used in most screening-level exposure analyses. However, exposure assessments have become increasingly complex, and probabilistic techniques may be useful when, for example, exposure parameters have large variability or when multiple sources exist (U.S. EPA, 2001b).

Based on the bounding assumptions used in this level of analysis and comparison with the hazard characterization (Section 4.1), a set of potentially significant exposure scenarios for relevant age groups will be identified. In the screening-level analysis, differences in exposure between children of different developmental stages are identified. For some specific exposure scenarios and compounds, combining or subdividing some of the age groups may be appropriate, for example, where variation in exposure factors and resulting exposures is insignificant (U.S. EPA, 2005e).

Limited data may be an impediment in conducting accurate lifestage-specific assessments, and for making decisions regarding combining or eliminating age groups. When making an assessment and limited data is available, the assessor should use the recommended age groups (U.S. EPA, 2005e) as a starting point. Then, based on qualitative information, the assessor can determine if little variability is expected among some age groups, in which case the age bins can be combined. If data are not available to make this determination, then this can be described as an area of uncertainty and identified as an area for future research. A possible approach to estimating exposure factors and dose when data are not available uses age-dependent curve fitting to help fill in the data gaps. Any assumptions used in assessing exposure for a particular age bin should be discussed in the assessment.

Once screening-level estimates of exposure are developed for each scenario and each age group, the questions in Table 4-9 could be considered. In order to identify and understand the importance of parameters and uncertainties in these exposure estimates, a sensitivity analysis is generally conducted on the potentially significant scenarios. For a screening assessment to have value, the potential range of parameter values is considered when conducting the sensitivity analysis (e.g., some parameters can vary only between 0 and 1; others can vary by three orders of magnitude). In addition, the uncertainty associated with assumptions that are based on little or no data would need to be evaluated before any conclusions about the level of "conservatism" can be made. Methods for conducting a sensitivity analysis are discussed further in Section 4.3.5.

4.3.3.2.2. *Refined assessment.* This tier of the analysis level provides more detail for potentially relevant scenarios and potentially vulnerable age groups. The goal of this tier is often to estimate the distribution of exposure for the relevant lifestages. Based on results of the sensitivity analysis conducted for the screening-level assessment, significant exposure factors and important assumptions are revisited to develop more realistic estimates of exposure.

This more advanced analysis may include the application of sophisticated modeling tools to develop exposure estimates for use in regulatory decisions. A variety of modeling tools have been developed over the years to facilitate exposure assessment (Price et al., 2003, and references therein for review of available tools). Some of the types of models available include total source models (e.g., aggregate and cumulative models developed to meet requirements of FQPA); multi-route models of exposure (e.g., local waste site models, tap-water exposure models), models of exposures to specific sources or routes (e.g., dietary models, consumer product models), indoor air models, and occupational models. Few of these models are designed currently to specifically address lifestage exposures. As a result, data on the age bins used in the models and outputs produced by the models may not address the specific age groups of interest for a complete lifestage-specific assessment. This issue is discussed further in *Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants* (U.S. EPA, 2005e).

Limitations of the data, model results, and associated uncertainties remaining in the refined tier are considered and addressed in this analysis. Available exposure data sets may not

allow modelers or risk assessors to directly extract data from the underlying sources to conduct lifestage-specific analyses. Potential approaches to address this issue include the following:

- reorganizing the exposure input data set to conform to the age groupings;
- using probabilistic sampling techniques to go beyond the categorical limits of the underlying database to utilize all the data, and then formatting the probabilistic model output into the desired age groupings to represent exposure doses; and
- developing a weighting scheme for the underlying data set to align it with the desired age groupings.

The exposure data may need to be statistically weighted so that equal weight is given to all ages within the group when estimating the group mean and variability statistics.

4.3.3.2.3. *Supplemental data collection.* Based on results of the refined assessment and the associated sensitivity and uncertainty analyses, specific data needs may be identified. If the objectives of the risk assessment indicate that any specific uncertainties in the exposure characterization be addressed, collection of new data to address them may be needed and additional analyses conducted.

Table 4-9. Examples of lifestage-specific questions for exposure analysis level or tiered assessment.

Topic	Lifestage-Specific Question(s)
Screening Assessment (Section 4.3.3.2.1)	Do these results address the questions posed in the problem definition phase of the risk assessment?
	What are the bounding assumptions used to identify relevant sources, pathways, and scenarios?
	What is the potential magnitude of exposures?
	How do potentially relevant scenarios and potentially vulnerable age groups compare with critical windows identified in the hazard characterization?
	How do these lifestages compare to the critical windows identified based on the TK and TD vulnerabilities (Section 4.1)?
	How do potential exposure levels compare with hazard levels (e.g., MOE)?
	Which exposure factors drive the results of the screening assessment and why?
	What is the potential variability of exposure factors (e.g., orders of magnitude vs. factor of 2 or 3)?
	Is the available exposure information adequate? What criteria are used to determine adequacy? What are the significant exposure data needs that may require additional exposure data?
Refined Assessment (Section 4.3.3.2.2)	Were the exposure data adequate to sufficiently investigate and identify relevant differences across age groups?
	What is the central tendency of the distribution of the exposure when compared with the high-

	end exposures?
	How do potential exposure levels compare with dose-response characterization results?
	Which developmental stage of children (age bins) represent the highest exposures?
	Is the available exposure information adequate for a more refined assessment? What additional criteria are used to determine adequacy? What are the significant exposure data needs that may require additional exposure data?
	What are the available exposure assessment models?
	Are distributions available for exposures of interest (e.g., by media, source, pathway)? If not, do they need to be developed? Are there sufficient data for their development?
	How will variability and uncertainty be addressed?
	What are the time patterns of exposure?
	How will exposure monitoring data, PBTK modeling, and biomonitoring data be incorporated?
	What are the additional stressors and their cumulative impact?
Supplemental Data Collection (Section 4.3.3.2.3)	Have any critical data needs been identified?

4.3.4. Variability Analysis

Variability refers to the inherent lack of uniformity in a population that cannot be reduced with additional data but can be presented by providing ranges or distributions of the exposure. Differences among individuals in a population are referred to as inter-individual variability. Differences associated with an individual over time are referred to as intra-individual variability.

Among children, inter-individual variability is due to rapid physiologic and behavioral changes. Even within a relatively narrow age group, variability may be large. For oral and dermal exposures, variability in exposure/dose is due to factors such as gross motor development, fine motor development, cognitive development, and social development. For inhalation exposures, relevant factors influencing variability in exposure/dose include, for example, activity level and breathing behavior (e.g., the transition from mouth to nasal breathing) (U.S. EPA, 2005e). Infants may be breast-fed or bottle-fed. Young children may have higher contact with surfaces than do older children and they explore their environment by mouthing objects. Physiologic characteristics affecting variability in exposure/dose include anatomical characteristics (e.g., body weight and proportion of body fat) and specific organ and physiologic systems. For example, infants have immature immune systems, and renal functions are less than those predicted by surface area (U.S. EPA, 2005e).

This variability affects the determination of upper percentiles of exposure and its associated risk. That is, given a high-quality/high-quantity set of data for each age group, there may still be significant variability for a particular exposure factor, set of factors, or exposure pathway. The better the data and the characterization of this variability, the better the basis for final selection of age groups for a specific assessment. Example questions are presented in Table 4-10.

4.3.5. Sensitivity Analysis

Sensitivity analysis is defined as the assessment of the impact of changes in input values on model outputs. Its main purpose in any exposure characterization is to determine which variables in the model equations and what pathways or scenarios most affect the exposure estimate. These techniques can also be used to assess key sources of variability and uncertainty for the purpose of prioritizing additional data collection or research. This is particularly relevant in children's assessments because they are often based on limited data. Because the variables of particular interest are those that have an impact on lifestage-specific estimates, the sensitivity analysis may need to focus considerable attention on the impact of exposure factors related to children's behavior. These factors affect the exposure patterns in space and time and are also typically the most uncertain. Example questions are presented in Table 4-10.

4.3.6. Uncertainty Analysis

Uncertainty is described as a lack of knowledge about factors affecting exposure or risk. Uncertainty in the exposure estimates may be a result of limited data for significant exposure factors for a particular age group. Uncertainty may also be due to assumptions made in development of the model. For example, soil ingestion studies in the literature have focused on children between 2 and 7 years of age, resulting in a lack of data for children less than 2 years of age. Uncertainties are acknowledged and characterized to the extent possible.

Probabilistic assessments can be useful statistical tools for analyzing variability and uncertainty in risk assessments, given that adequate data are available. The Monte Carlo analysis can be used to better characterize variability and uncertainty across the population, and to compare one lifestage (e.g., infants) to another (e.g., adults). General issues to consider when applying these quantitative methods are described in EPA's *Guiding Principles for Monte Carlo*

Analysis (U.S. EPA, 1997b). The EPA sponsored workshop in 1998 discussed issues regarding the selection of input distributions for probabilistic assessments (U.S. EPA, 1999b). Methodologies for selecting parametric distributions to be used in probabilistic assessments are described in *Options for Developing Parametric Probability Distributions for Exposure Factors* (U.S. EPA, 2000b). Example questions are presented in Table 4-10.

Table 4-10. Examples of lifestage-specific questions for exposure variability, sensitivity, and uncertainty analyses.

Topic	Lifestage-Specific Question(s)
Variability Analysis (Section 4.3.4.)	If different approaches were used to estimate exposure for different lifestages or within a lifestage, what were the results? Can they be compared and, if so, how do they compare? Which approach is more appropriate?
	Does the lifestage-specific assessment capture the variability in the exposed groups? What are the ranges or distributions of exposure?
	What are the route, level, timing (i.e., lifestage), and duration of exposure used in the experimental animal studies as compared with expected human exposures?
	Are the available data from the same route of exposure as the expected human exposures? If not, are TK data available to extrapolate across routes of exposure?
	Are experimental animal data available from the same lifestages as the expected exposed human lifestage? If not, are TK data available to extrapolate across species and lifestages?
	What information was used to support duration adjustment and to calculate the human equivalent concentration or dose?
	How far does one need to extrapolate from the observed data to environmental exposures (i.e., MOE)? One, two or multiple orders of magnitude? What is the impact of such an extrapolation?
Sensitivity Analysis (Section 4.3.5)	What parameters have the greatest influence on the exposure model outputs?
	What is the adequacy of the data for the parameters that are identified in the sensitivity analysis as the most important parameters?
Uncertainty Analysis (Section 4.3.6.)	What are the uncertainties in the estimates, both within and across lifestages?
	What are the data limitations and how do they compare across lifestages?
	What data gaps exist, both within and across lifestages? How significant are these data gaps? How sensitive are the results to these data gaps?
	Is it feasible or desirable to collect more data pertaining to particular lifestages? Could the exposure estimates be refined if more data were available?

4.3.7. Iteration with Hazard and Dose-Response Characterization

Following exposure characterization, coordination, and communication with the hazard and dose-response assessors (Sections 4.1 and 4.2) may be useful. For example, if a screening-level analysis revealed that the 0–1 year age bin was more highly exposed due to nursing ingestion than was any other lifestage, an assessor may be prompted to re-evaluate hazard and

dose-response characterization to make sure that potential vulnerabilities during this age window are well understood or if further data needs could be identified.

4.3.8. Lifestage-Specific Exposure Characterization Narrative

The results of the exposure characterization are summarized in a narrative that includes a discussion of the results, analysis, and conclusions. The narrative includes a discussion of the key assumptions, limitations, and uncertainties associated with the exposure estimates and any potential bias in the results. Variability analysis (Section 4.3.4), sensitivity analysis (Section 4.3.5), and uncertainty analysis (Section 4.3.6) are summarized. It is useful to also include a description of how the exposure characterization can be improved and uncertainties be reduced by additional research or collection of data. Through this narrative, the results of the exposure characterization are communicated in a clear and concise manner to the risk manager. These results include considerations of childhood variability and uncertainty within the exposure characterization.

The focus of the exposure characterization is to identify age groups and address vulnerability resulting from differential exposure. It is impossible to completely separate consideration of exposure and potential dose from consideration of internal dosimetry and response; therefore hazard characterization (Section 4.1), dose-response characterization (Section 4.2), and exposure characterization are intimately linked. For example, information on exposure scenarios of a compound to humans ensures that hazard information is relevant to the measured exposure. Also, understanding the dosimetry of an absorbed agent can inform the temporal resolution needed in the exposure data and characterization. Some questions to consider when summarizing the exposure characterization narrative include the following:

- What is the basis for the exposure characterization (i.e., monitoring, modeling, or other analyses of exposure distributions)?

- How was the central tendency estimate developed? What factors or methods were used in developing this estimate?

- How was the high-end estimate developed? What factors or methods were used in developing this estimate?

- How do the adverse health effects identified in the hazard characterization phase (Section 4.1) inform the identification of exposures of greatest relevance for the observed outcomes?

- How do patterns of exposure (continuous vs. intermittent) and half-life in the body influence the health outcome? What are the exposures during critical windows in development?

- Are there particular developmental stages during which children are highly exposed? Do health outcomes vary during different developmental periods? How does this inform identification of the exposures of greatest biological significance for the observed outcomes?

- How does information on dosimetry indicate the level of temporal resolution needed in exposure data and modeling? What dose metrics are being considered for child-related assessments?

- How does the fate of the agent being evaluated affect exposure in children? Are children exposed to other agents with a similar MOA to the one being assessed? Is sufficient MOA information available to consider a cumulative exposure assessment?

5. LIFESTAGE-SPECIFIC RISK CHARACTERIZATION

Risk characterization is the final phase of the risk assessment process (Figure 5-1). This final phase of the risk assessment utilizes the information from the problem formulation (Chapter 3) and analysis (Chapter 4) phases. After risk characterization is put into context (Section 5.2), the information is utilized in risk communication and risk management.
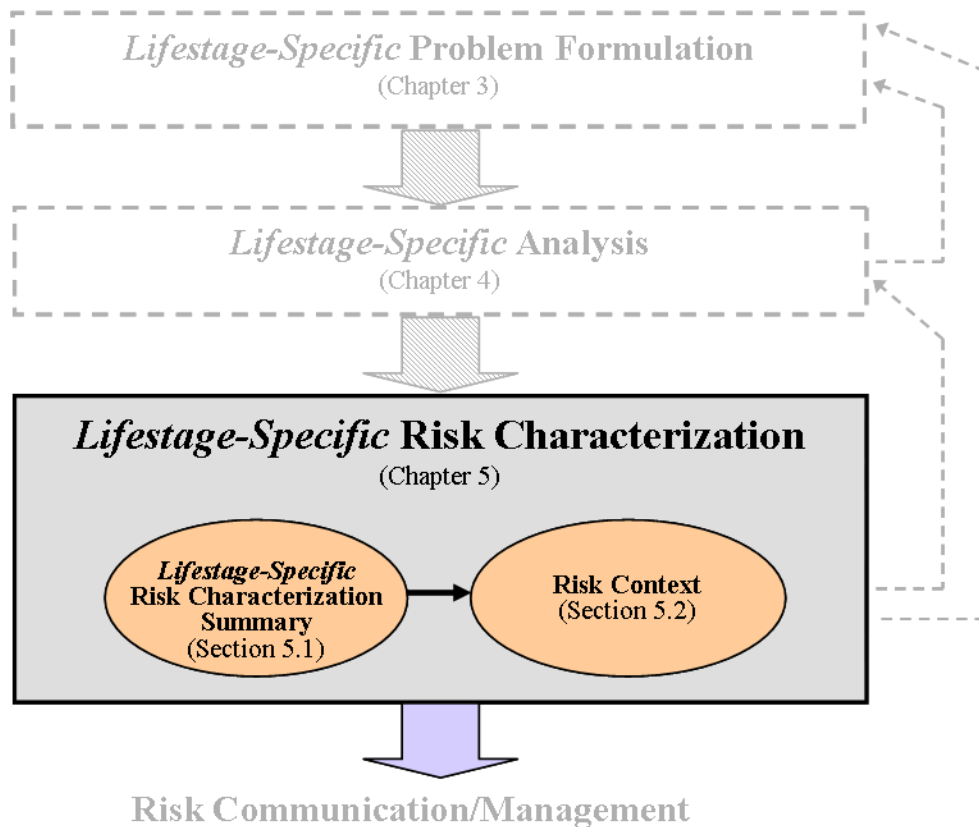
Figure 5-1. Flow diagram for lifestage-specific risk characterization.

The risk characterization describes the overall picture of health risks resulting from children's exposures, in which the hazard characterization (Section 4.1), dose-response characterization (Section 4.2), and exposure characterization (Section 4.3) components of the analysis phase are integrated and summarized. Major non-technical conclusions are drawn that inform the risk managers, who will make risk decisions in context with the problem identified in problem formulation (Chapter 3).

During hazard characterization (Section 4.1), an assessor evaluates and describes the information on the capacity of an environmental agent's exposure during developmental lifestages to cause outcomes at any lifestage in both laboratory animals and humans. The qualitative WOE evaluation is based both on the type and quality of data derived from humans and laboratory animals and on the integration of ancillary data (SAR, genetic toxicity, TK, TD, and MOA).

The dose-response characterization (Section 4.2) focuses on quantitative relationships between exposure during developmental lifestages of concern and critical outcomes during lifestages of concern identified in the hazard characterization (Section 4.1). Methods for assessing dose-response relationships often depend on assumptions used in the absence of data. Thus, assumptions are clearly articulated in the risk characterization section.

The exposure characterization (Section 4.3) describes the basis for values used in exposure scenarios. Exposure estimates are based on a combination of available data and assumptions. In exposure characterizations, the quality and representativeness of the available data are discussed. Then, in turn, the assumptions made, the general logic to develop these assumptions, and the effect that they may have on the results are also discussed. The major factors considered to contribute to the greatest uncertainty in the exposure characterization are described and linked to information from sensitivity analyses. Lack of exposure data or limitations of specific types of data are described.

Detailed guidance on integration of these analysis steps into a risk characterization is provided in EPA's *Science Policy Handbook: Risk Characterization* (U.S. EPA, 2000e). Other sources of information that provide guidance regarding children's health risk assessment include the EPA guidelines for developmental toxicity (U.S. EPA, 1991), reproductive toxicity (U.S. EPA, 1996), neurotoxicity (U.S. EPA, 1998b), and cancer risk assessment (U.S. EPA, 2005a,b). In addition, the NRC report Science and Judgment in Risk Assessment (NRC, 1994) provides additional information about the risk characterization process.

The issues to be addressed in risk characterization are provided in example questions, with an emphasis on lifestage-specific issues, to guide the assessor through this process. The information to answer these questions is derived from the analysis phase (Chapter 4) and used in the risk characterization. The questions that follow are a modification of those presented in EPA's *Science Policy Handbook: Risk Characterization* (U.S. EPA, 2000e) and those developed

for risk characterization within the *Guidelines for Reproductive Toxicity Risk Assessment* (U.S. EPA, 1996).

5.1. LIFESTAGE-SPECIFIC RISK CHARACTERIZATION SUMMARY

A lifestage-specific risk characterization includes a concise description of the key qualitative and quantitative aspects of the analysis. This includes a discussion of the critical windows for duration and timing of exposure and outcome. Then, the assessor identifies and describes the assumptions, uncertainties, and significant data gaps that could affect the major conclusions. Finally, the summary includes a qualitative and quantitative justification for the application of lifestage-specific adjustments for duration-specific health values (e.g., use of lifestage-specific RfV for a specific duration of exposure) if the assessment warrants it. Three basic questions this Framework highlights are (U.S. EPA, 2000e, p.39)

- Have the potential hazards to children been adequately characterized?
- Were the potential hazards incorporated into dose-response characterization (Section 4.2)?
- Have the exposures to children been adequately characterized?

5.1.1. Key Information from the Analysis Phase

The assessor reviews the narratives for the three analysis steps of the risk assessment (Chapter 4) in order to determine the key information relevant to children's risk. In the narrative, the assessor identifies the key studies, summarizes the WOE, presents the justification for the calculated major risk estimates, and articulates the defaults and assumptions. The assessor considers how the key information from the analysis phase relates back to the purpose and scope of the assessment. The following are sample questions to ask when considering the key information from the analysis phase of the assessment:

- What lifestages were assessed? Are there any highly exposed subgroups?
- What are the most significant lifestage-specific exposure scenarios? What are the ranges of exposures?
- What are the critical effects observed following developmental lifestage exposures? Do they differ qualitatively and/or quantitatively from adults who are exposed?

- How were the exposure scenarios and lifestage(s) accounted for in dose-response characterization (Section 4.2)?

- What are the key studies for TK, TD, and MOA? Does available MOA information aid in the interpretation of the hazard data for different lifestages? What are the implications of the hypothesized MOAs for potential adverse effects and their relationship to risk?

5.1.2. Scientific Assumptions

During risk characterization, scientific assumptions and defaults used in the analysis phase (Chapter 4) are described. An example of an assumption is using a ¾ body weight scaling for inhalation dosimetry in children (U.S. EPA, 2006d). It is important to transparently document these assumptions and rationale for decisions made in the assessment.

- What are the major scientific assumptions related to children's risks and how are they addressed?

- Was SAR information or MOA information used to bridge chemical-specific data gaps for specific lifestages of concern?

5.1.3. Risk Drivers

The development of MOE or hazard quotients for critical effects that might occur during specified exposures scenarios for certain lifestages may provide worst case scenarios and provide some appreciation of relative risk for different adverse outcomes for different exposure scenarios.

- What are the risk drivers, and what are the policy implications?

- Are specific exposure scenarios during specific lifestages major risk drivers?

- Are specific critical windows of exposures contributing to the critical outcomes that are the major risk drivers?

5.1.4. Strengths and Weaknesses

Characterizing the strengths and weaknesses of the database is central to a lifestage-specific risk characterization. In many cases, the information on outcomes following exposure during developmental lifestages will be very limited but substantial enough to invoke concern or consideration of the strengths of the database. Weaknesses in the database will influence the lifestage-characterization of the variability (Section 5.1.4.1), sensitivity (Section 5.1.4.2), and uncertainty (Section 5.1.4.3). Integration of the WOE evaluation (Section 4.1.3.1) with the

variability, sensitivity, and uncertainty analyses for dose-response (Sections 4.2.5, 4.2.6, and 4.2.7) and exposure (Sections 4.3.4, 4.3.5, and 4.3.6) provide further characterization and integration of the strengths and weaknesses of the overall assessment. This summary strives for balance by describing the areas of confidence and uncertainty in the assessment.

5.1.4.1. *Variability*

Explicit acknowledgment of sources of variability is considered in the risk characterization phase. By summarizing the findings from the variability analyses conducted in the analysis phase (Sections 4.1.2.9, 4.1.3.1.2.1, 4.2.5, and 4.3.4), it may be possible to determine whether different approaches provide similar risk estimates. Answers to the following questions may be helpful to describe the overall variability of the assessment:

- Does the assessment capture the variability in the exposed population? How is variability addressed?

- Who is most at risk (e.g., physiologically, genetically, highly exposed)?

- What is the relevance of experimental animal studies to humans at particular lifestages?

- What are the limitations of the data available regarding variability? What data gaps related to variability exist?

- Are there biological, behavioral, ethnic, racial, or socioeconomic factors that may affect variability in human exposure or response?

5.1.4.2. *Sensitivity*

The findings from the sensitivity analyses conducted in the analysis phase (Sections 4.2.6 and 4.3.5) are summarized in the risk characterization phase in order to underscore the strengths and the weaknesses related to the derivations of health values and exposure values in the assessment. Answers to the following questions may help describe the overall sensitivity of the assessment:

- What parameters have the greatest influence on the dose-response and exposure model outputs?

- Are the parameters to which a model is most sensitive likely to vary across lifestages? What is the likely impact of such differences on model predictions on defining variability or uncertainty in the assessment?

- What are the limitations of the data available regarding sensitivity? What data gaps related to sensitivity exist?

5.1.4.3. *Uncertainty*

Uncertainty originating from various data sources can have an impact on risk analysis. Explicit acknowledgment of sources of uncertainty described in the analysis phase (Sections 4.1.2.10, 4.1.3.1.2.2, 4.2.7, and 4.3.6) is considered when integrating the uncertainties in the risk characterization. This summary includes clear and concise statements about the limitations of the data from the analysis phase for this lifestage-specific assessment and may include discussion of uncertainties in other related assessments. Critical data gaps, defined by the impact they have on the risk assessment, are identified and described. These critical data gaps may require consideration and application of uncertainty factors (e.g., database UF). In addition, uncertainty or critical data gaps may suggest further studies that may provide new information or insight to reduce uncertainties in a future risk assessment. Answers to the following questions may prove helpful in describing the overall uncertainty of the assessment:

- What are the uncertainties in the assessment for different lifestages of development? How are these uncertainties addressed?

- How are the limitations of the available data related to uncertainty? What significant data gaps exist relevant to uncertainty? How do these impact the magnitude of uncertainty in the assessment?

- What are the priority data-needs studies that could produce information that may reduce uncertainties in lifestage-specific risk assessment?

- What are the degrees of confidence in the dose-response and exposure model(s) that are used to derive risk values?

5.1.5. Key Conclusions

A description of critical effects and the supporting evidence for these conclusions is included in this section. Attendant risk numbers or a range of risk values for the critical effects can illustrate some degree of certainty for the key conclusions. For outputs of this analysis to be most useful in benefits analysis (Chapter 3), the outcomes that are quantified are expressed as changes in adverse outcomes or precursor effect (e.g., change in incidence of illness or symptoms) that are readily understood by the public. Reliance on single point risk estimates for key conclusions may not be very useful for benefits analysis.

- What are the major qualitative conclusions regarding risk from developmental exposure? What is the degree of confidence in the conclusions?

- What are the quantitative estimates of the risk from developmental exposure? How do risks compare across lifestages? What is the degree of confidence in the risk estimates?

- Are there any broad risk implications for classes of compounds (e.g., SAR-related, same MOA)? Lifestages (e.g., in male fetuses, the period of sexual differentiation *in utero* is sensitive to exposure to anti-androgens)?

5.1.6. Alternative Risk Estimates Considered

Consideration of alternative hypotheses to explain lifestage-specific outcomes and the related exposures (Section 4.1.3.1.7) is part of transparency. Principles of parsimony (economy or simplicity of assumptions in logical formulation) should be considered in the presentation of alternatives and related to the lifestage-specific data that exist. The following examples are questions to consider regarding alternative risk estimates:

- What are the results of different analysis approaches (i.e., modeling, monitoring, and probability distributions)?

- Were adults considered to be more or less sensitive than other lifestages?

- What is the relative difference in the final risk value when using adult versus developmental lifestages of exposure? What is the relative difference in the final risk value when using a default versus a data rich approach?

- Are alternative hypotheses considered that might explain the observed lifestage-specific outcomes? Does an alternative hypothesis provide different risk estimates than the primary hypothesis?

5.1.7. Research Needs

The characterization of risk in many cases reveals lifestage-specific data gaps, but not all of these data gaps may translate into critical research needs. Research needs may be based upon qualitative or quantitative considerations in the database and the prioritization of research needs helps determine whether specific new data could potentially reduce uncertainty in the assessment. Questions to consider when assessing research needs for characterizing variability and uncertainty in risk estimates include the following:

- What are the priority lifestage-specific research needs? Are these chemical-specific, chemical class-specific, or basic research needs?

- Can priorities be assigned if more than one lifestage-specific research need is identified?

- Can the impact of the research be estimated (e.g., reduction of uncertainty in the assessment)?

- What are the key sources of variability, sensitivity, and uncertainty for the purpose of prioritizing additional data collection or research?

5.2. RISK CONTEXT

The risk characterization is anticipated to provide an answer to the problem formulation (Chapter 3), which may have included an initial screening of risk for prioritization and a preliminary estimation of risk). If the statement of the problem evolved during the analysis phase (Chapter 4), then this process is summarized in the risk characterization phase.

The risk estimates in this lifestage-specific assessment are described in the context of other similar or related risk assessments. The science policy assumptions employed in this assessment are clearly articulated in order to compare with previous decisions. Discussion of alternative hypotheses, alternative MOAs, and alternative risk estimates can be included to provide context to other previous risk decisions. The risk context could include discussion of cumulative and multiple exposures and their potential impact on a common MOA(s).

The risk context can also provide background for developing risk communication materials, which could include risk perception in light of related or prior risk decisions. Questions regarding risk context include the following:

- Where appropriate, can this risk be compared with other risks characterized by EPA or by other federal or state agencies? Have these other previous assessments reached similar or significantly different conclusions? What are the limitations of making these comparisons?

- What science policy (default) assumptions were employed in each of the three steps of the analysis phase?

- What were the scientific assumptions in each of the three steps of the analysis phase that may have policy implications?

- What alternative hypotheses were evaluated? What is the justification for the decision to choose one hypothesis over another?

- Is there reason to be concerned about cumulative or multiple exposures to classes of agents with a similar mechanism or MOA?

- Are there significant community concerns or common risks with which people may be familiar that may influence public perception of risk to children?

- Is the risk characterization information presented in a way that could be used for benefit analysis?

- Is the risk characterization information presented in a way that could be used for benefit analysis?

6. SUMMARY AND IDENTIFICATION OF GAPS IN APPROACHES FOR CHILDREN'S HEALTH RISK ASSESSMENT

This Framework summarizes the process for assessing health risks resulting from children's exposure to environmental agents using a phased approach that includes problem formulation (Chapter 3), analysis (Chapter 4), and risk characterization (Chapter 5). It uses many EPA documents that have outlined similar risk assessment approaches (U.S. EPA, 1998a, 2003a) and a workshop report that identified the need for and began the development of an approach to assessing children's risk from environmental exposures (ILSI, 2003).

This Framework is a conceptual overview of the considerations for evaluation of early life exposures and subsequent outcomes and does not constitute EPA guidance defined as a step-by-step process or standard operating procedure. This overview is accomplished by posing targeted questions to address each phase of the process and by referencing appropriate guidelines, guidance documents, and other relevant reports and literature. These references, including several EPA risk assessment guidelines related to health risks from children's exposures, can be drawn upon for more detailed information. One of the most relevant references is the *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991) that focuses primarily on the effects of prenatal exposures and, to a limited extent, on postnatal exposures and outcomes. Other EPA guidelines or guidance are focused on system- or disease-specific issues that include the effects of developmental exposures, specifically reproductive toxicity (U.S. EPA, 1996), neurotoxicity (U.S. EPA, 1998b), and cancer (U.S. EPA, 2005a,b). Guidelines or guidance on the effects of developmental exposures on other systems (e.g., respiratory, immune, renal, hepatic, cardiovascular, and, to some extent, endocrine) or outcomes (e.g., biomarkers of exposure or effect, toxicogenomics data) are lacking.

The relevance of specific developmental exposures on latent outcomes for application to risk assessments for various durations of exposure (i.e., acute, short term, and subchronic) is considered in many of the risk assessments currently being generated across EPA, although this issue has not been thoroughly explored to date. The document *A Review of the Reference Dose and Reference Concentration Processes* previously identified data needs and alternative approaches and strategies for developing testing guidelines; these have not yet been addressed and are reiterated below (U.S. EPA, 2002a, Section 5). In addition, there is a need for focused guidance on dose-response assessment after developmental exposures, despite the fact that a

good deal of research and methods development on BMD (U.S. EPA, 2000d) and biological modeling (Clewell et al., 2002a; Ginsberg et al., 2004b; Lau et al., 2000, 2001; Setzer et al., 2001) has been done using developmental data in experimental animals and humans. With regard to exposure assessment, there is limited EPA guidance on approaches specific to children at different lifestages, with the exception of the interim document *Child- Specific Exposure Factors Handbook* (U.S. EPA, 2002c) and the *Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants* (U.S. EPA, 2005e). Methods for both screening level and more detailed quantitative estimates of children's exposures are needed. Data for the recommended age groups (U.S. EPA, 2005e) are limited or nonexistent for some exposure factor determinations. The *Framework for Cumulative Risk Assessment* (U.S. EPA, 2003a) addresses generic concepts and approaches to evaluate cumulative risk; however, there is no specific guidance on developmental lifestage risk from cumulative exposures.

The integration of toxicity data and children's exposure estimates is an area for which no guidance exists but is needed. This integration is important because one exposure can lead to multiple outcomes, particularly for developmental exposures. In addition, the characteristics for each age group of concern to environmental agents can differ significantly for exposure and susceptibility. Therefore, guidance is also needed on using information on biological processes underlying development, MOA information, chemical-specific mechanisms, and anatomical, physiological, and behavioral characteristics at different developmental lifestages to determine critical times for exposure and the corresponding outcomes of concern.

At this time, significant research questions remain unanswered on the use of available exposure data to assess children's risk, such as

- How can biomonitoring data be interpreted to characterize exposure? How can available adult biomonitoring data be applied to children?

- How can available data from children be interpreted across developmental stages for which there are limited data?

- How can activity pattern data be used to classify children for exposure characterization?

- What resources or approaches can one use to address risk methodology for extrapolating inhalation dose to developmental lifestages?

- Can guidance be developed on incorporating critical window of vulnerability to reduce uncertainty, specifically for the time frame over which exposure should be averaged?

- How can risks be extrapolated to developmental exposure to non-genotoxic carcinogens?

- How can developmental lifestage-specific MOAs influence latent expression of adverse outcomes?

- Since TK and TD in children can rarely be studied, how can model variability in internal dose and sensitivity to toxicant action be better characterized?

Many of these questions are actively being investigated. These efforts will likely contribute to future guidance and policy papers on specific issues related to children's exposure and subsequent outcomes.

GLOSSARY

Activity Pattern Data – Information on human activities used in exposure assessments. The information may include a description of the activity, frequency of activity, duration spent performing the activity, and the microenvironment in which the activity occurs.

Adverse Effect – A biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism or reduces an organism's ability to respond to an additional environmental challenge.

Age-Dependent Adjustment Factors (ADAF) – Adjustments to cancer slope factors that recognize the increased susceptibility to cancer from early life exposures to mutagens in the absence of chemical-specific data.

Area Under the Curve (AUC) – The area of the time x concentration curve that helps to define the internal dose.

Benchmark Dose (BMD) – A dose that produces a predetermined change in response rate of an adverse effect (called the benchmark response or BMR) compared to background.

Benchmark Dose Lower Confidence Level (BMDL) – A statistical lower confidence limit on the dose at the BMD.

Benefits Analysis – A method that develops monetary values comparing costs and benefits to inform the policy making process (U.S. EPA, 2000a).

Bias – A trend in methodology or analysis that can lead to systematic deviations from the true data.

Biologically Based Dose-Response (BBDR) Model – A predictive model that describes biological processes at the cellular and molecular level linking the target organ dose to the adverse effect.

Biomarker – A biological molecule or biochemical indicator of exposure or biological changes resulting from exposures, or markers of risk or susceptibility.

Biomonitoring – The assessment of human exposure to chemicals by the measurement of the chemicals or their metabolites (breakdown products) in human tissues or fluids such as blood or urine. Blood and urine levels reflect the amount of the chemical in the environment that actually gets into the body.

Body Burden – The amount of a particular chemical, especially a potentially toxic chemical, stored in the body at a particular time as a result of exposure. Body burdens can be the result of long-term or short-term storage, e.g., the amount of a metal in bone, the amount of a lipophilic

substance such as PCB in adipose tissue, or the amount of carbon monoxide (as carboxyhemoglobin) in the blood.

Bounding Estimate – An estimate of exposure, dose, or risk that is higher than that incurred by the person in the population with the highest exposure, dose, or risk. Bounding estimates are useful in developing statements that exposures, doses, or risks are "not greater than" the estimated value.

Cancer – A disease of heritable, somatic mutations affecting cell growth and differentiation and characterized by an abnormal, uncontrolled growth of cells.

Case-Control Study – An epidemiologic study that compares subjects with the disease of interest (cases) to subjects without the disease (controls). The groups are compared with respect to exposure history to ascertain whether they differ in the proportion exposed to the chemical(s) under investigation.

Case Report – A description of a person in a population or study group identified as having a particular disease, health disorder, or condition under investigation, without a comparison made to a control.

Child – Conception to maturation of all organ systems, approximately 21 years of age.

Concentration – The ratio of the mass or volume of a solute to the mass or volume of the solution or solvent.

Conceptual Model – A written description or a visual representation of actual or predicted relationships between humans or ecological entities and the chemicals or other stressors to which they may be exposed.

Confounder (or Confounding Factor) – A condition or variable that is both a risk factor for disease and is associated with an exposure or outcome of interest. This association between the exposure of interest and the confounder may make it falsely appear that the exposure of interest is associated with the outcome.

Critical Effect – The first adverse effect, or its known precursor, that occurs to the most sensitive species as the dose rate of an agent increases.

Critical Window of Exposure – Developmental period when vulnerability to exposures is increased and can result in developmental effects.

Cumulative Impact – The combination of aggregate exposures to multiple agents or stressors.

Detoxification – Process of chemical modification that make a toxic molecule less toxic.

Dose – The amount of a substance available for interaction with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism.

- *Absorbed Dose* is the amount crossing a specific absorption barrier (e.g., the exchange boundaries of skin, lung, and digestive tract) through uptake processes.
- *Biologically Effective Dose* is the amount of the chemical available for interaction by any particular organ or cell.
- *Internal Dose* is a more general term denoting the amount absorbed without respect to specific absorption barriers or exchange boundaries.
- *Potential Dose* is the amount ingested, inhaled, or applied to the skin.

Dose Metric – The target tissue dose that is closely related to ensuing adverse response. Dose metrics reflect the biologically active form of the chemical, its level, and duration of exposure, and its intensity. Examples of units of measurement for dose are AUC, maximum concentration.

Dose-Response Assessment – The determination of the relationship between the magnitude of administered, applied, or internal dose and a specific biological response. Response can be expressed as measured or observed incidence, percent response in groups of subjects (or populations), or the probability of occurrence of a response in a population.

Dose-Response Curve – A graphical representation of the quantitative relationship between administered, applied, or internal dose of a chemical or agent, and a specific biological response to that chemical or agent.

Dosimetric Adjustment Factor (DAF) – A multiplicative factor used to adjust observed experimental or epidemiological data to human equivalent concentration for assumed ambient scenario.

Dosimetry – A process of measuring or estimating dose.

Effect Modifier – A variable that modifies the outcome of interest by a greater (synergistic) or lesser (antagonistic) effect. An effect modifier can be identified through stratification of the data.

Environmental Fate – The destiny of a chemical or biological pollutant after release into the environment. Environmental fate involves temporal and spatial considerations of transport, transfer, storage, and transformation.

Epidemiology – The study of the distribution and determinants of health-related states or events in specified populations.

Exposure – Contact made between a chemical, physical, or biological agent and the outer boundary of an organism. Exposure is quantified as the amount of an agent available at the exchange boundaries of the organism (e.g., skin, lungs, gut).
- *Acute Exposure* is exposure by the oral, dermal, or inhalation route for 24 hours or less.
- *Chronic Exposure* is repeated exposure by the oral, dermal, or inhalation route for more than approximately 10% of the life span in humans (more than approximately 90 days to 2 years in typically used laboratory animal species).

- *Intermittent Exposure* is a repeated exposure in which there is no effect of one exposure on the effect of the next; this definition implies sufficient time for the chemical and its metabolites to subchronic clear the biological system before the subsequent exposure (i.e., non-cumulative toxicokinetics).
- *Longer-Term Exposure* is repeated exposure by the oral, dermal, or inhalation route for more than 30 days, up to approximately 10% of the life span in humans (more than 30 days up to approximately 90 days in typically used laboratory animal species).
- *Short-Term Exposure* is multiple or continuous exposure to an agent for a short period of time, usually 1 week.

Exposure Assessment – An identification and evaluation of the human population exposed to a toxic agent that describes its composition and size and the type, magnitude, frequency, route, and duration of exposure.

Exposure Concentration – The concentration of a chemical in its transport or carrier medium at the point of contact.

Exposure Factor – Variables that define how exposure to a chemical or agent takes place (e.g., concentration, intake, body weight).

Exposure Media – Major environmental categories that surround or contact humans, animals, plants, and other organisms (surface water, ground water, soil, or air) and through which chemicals or pollutants move.

Exposure Pathway – The physical course a chemical or pollutant takes from its source to the organism exposed.

Exposure Route – The way a chemical or pollutant enters an organism after contact, e.g., by ingestion, inhalation, or dermal absorption.

Exposure Scenario – A combination of facts, assumptions, and inferences that define a discrete situation where potential exposures may occur. These may include the source, the exposed population, the time frame of exposure, microenvironment(s), and activities. Scenarios are often created to aid exposure assessors in estimating exposure.

Database (Extent of) **–** *Minimal Database* is a database in which no human data are available, and route-specific toxicity data are limited to dose-response data applicable to the duration in question with assessment of outcomes other than mortality. A study showing only effect levels for mortality or other extremely severe toxicity would not be sufficient to set a reference value. *Robust Database* is a database that includes extensive human and/or animal toxicology data that cover route-specific information on many health outcomes, durations of exposure, timing of exposure, lifestages, and susceptible subpopulations (see U.S. EPA, 2000b, pages 4-19).

Hazard Assessment – The process of determining whether exposure to an agent can cause an increase in the incidence of a particular adverse health effect (e.g., cancer, birth defect) and whether the adverse health effect is likely to occur in humans.

Hazard Characterization – A description of the potential adverse health effects attributable to a specific environmental agent, the mechanisms by which agents exert their toxic effects, and the associated dose, route, duration, and timing of exposure.

Human Equivalent Concentration (HEC) or Dose (HED) – The human concentration (for inhalation exposure) or dose (for other routes of exposure) of an agent that is believed to induce the same magnitude of toxic effect as the experimental animal species concentration or dose. This adjustment may incorporate toxicokinetic information on the particular agent, if available, or use a default procedure, such as assuming that daily oral doses experienced for a lifetime are proportional to body weight raised to the 0.75 power.

Intake Rate – Rate of inhalation, ingestion, and dermal contact, depending on the route of exposure. For ingestion, the intake rate is simply the amount of food containing the contaminant of interest that an individual ingests during some specific time period (units of mass/time). For inhalation, the intake rate is the rate at which contaminated air is inhaled. Factors that affect dermal exposure are the amount of material that comes into contact with the skin and the rate at which the contaminant is absorbed.

Key Event – A key event is an empirically observable precursor step that is itself a necessary element of the mode of action (U.S. EPA, 2005a,b). Toxicokinetic and toxicodynamic steps that lead to a toxic response can be considered as key event(s).

Lifestage Approach – The comparison of exposure and effect data across different lifestages from conception to old age. This approach provides a temporal context in which to evaluate data for risk assessment.

Longitudinal Study – An epidemiologic study comparing subject with an exposure of interest to those without the exposure. These two cohorts are then followed over time to determine the differences in the rates of disease between the exposure subjects.

Low-Dose Extrapolation – An estimate of the response at a point below the range of the experimental data, generally through the use of a mathematical model.

Lowest-Observed-Adverse-Effect Level (LOAEL) – The lowest exposure level at which there are biologically significant increases in frequency or severity of adverse effects among the exposed population when compared with an appropriate control group.

Margin of Exposure (MOE) – The ratio of the point of departure (POD) over an exposure estimate (MOE = POD/Exposure).

Mechanism of Action – The complete sequence of biological events (i.e., including toxicokinetic and toxicodynamic events) from exposure to the chemical to the ultimate cellular and molecular consequences of chemical exposure that are required in order to produce the toxic effect. However, events that are coincident but not required to produce the toxic outcome are not included.

Media – see Exposure Media.

Meta-Analysis – Any systematic method that uses statistical analysis to integrate the data from a number of independent studies.

Mode of Action – The sequence of key event(s) (i.e., toxicokinetics and toxicodynamics) after chemical exposure upon which the toxic outcome depend.

Model – A mathematical function with parameters that can be adjusted so that the function closely describes a set of empirical data. A mechanistic model usually reflects observed or hypothesized biological or physical mechanisms and has model parameters with real world interpretation. In contrast, statistical or empirical models selected for particular numerical properties are fitted to data; model parameters may or may not have real world interpretation. When data quality is otherwise equivalent, extrapolation from mechanistic models (e.g., biologically based dose-response models) often carries higher confidence than extrapolation using empirical models (e.g., logistic model).

No-Observed-Adverse-Effect Level (NOAEL) – The highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered adverse or precursors of adverse effects.

Outcome – A clinical manifestation of biological effects that results from an exposure.

Pathway – see Exposure Pathway.

Person-Oriented Model – An approach in which the individual's exposure-related characteristics are defined first and then used to determine the probability of the individuals' being exposed to a specific source and the resulting dose.

Physiologically based Toxicokinetic (PBTK) Model – A model that estimates the dose to a target tissue or organ by taking into account the rate of absorption into the body, distribution among target organs and tissues, metabolism, and excretion. (Also referred to as physiologically based pharmacokinetic model.)

Point-of-Contact Approach – An approach to quantifying exposure by taking measurements of concentration over time at or near the point of contact between the chemical and an organism while the exposure is taking place.

Point of Departure (POD) – The dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (BMD) or a NOAEL or LOAEL for an observed incidence, or change in level of response.

Portal of Entry – The point at which the contaminant enters the body (e.g., mouth, nose, skin).

Precursor Event – An early condition or state preceding the pathological onset of a disease.

Reference Concentration (RfC) – An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, a LOAEL, or a benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used. It is generally used in EPA's noncancer health assessments.

Reference Dose (RfD) – An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, a LOAEL, or a benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. It is generally used in U.S. EPA's noncancer health assessments.

Reference Value (RfV) – An estimation of an exposure for (a given duration) to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse effects over a lifetime. It is derived from a BMDL, a NOAEL, a LOAEL, or another suitable POD, with uncertainty/variability factors applied to reflect limitations of the data used.

Risk (in the context of human health) – The probability of adverse effects resulting from exposure to an environmental agent or mixture of agents.

Risk Assessment (in the context of human health) – The evaluation of scientific information on the hazardous properties of environmental agents (hazard characterization), the dose-response relationship (dose-response assessment), and the extent of human exposure to those agents (exposure assessment). The product of the risk assessment is a statement regarding the probability that populations or individuals so exposed will be harmed and to what degree (risk characterization).

Risk Characterization – The integration of information on hazard, exposure, and dose-response to provide an estimate of the likelihood that any of the identified adverse effects will occur in exposed people.

Risk Management (in the context of human health) – A decision-making process that accounts for political, social, economic, and engineering implications together with risk-related information in order to develop, analyze, and compare management options and select the appropriate managerial response to a potential chronic health hazard.

Route – see Exposure Route.

Structure-Activity Relationship (SAR) approach to toxicology screening – This approach elucidates the relationship between features of chemical structure and biological activity. It is based on the premise that the biological fate and activity of a chemical (i.e., whether it is absorbed, metabolized, or bioaccumulated and whether it interacts at a molecular level to exert a response) is ultimately determined by chemical structure.

Scenario Evaluation Approach – An approach to quantifying exposure by measurement or estimation of both the amount of a substance contacted and the frequency/duration of contact and subsequently linking these together to estimate exposure or dose.

Sensitivity Analysis – Refers to the variation in output of a model with respect to changes in the values of the model input(s). Sensitivity analysis can provide a quantitative ranking of the model inputs based on their relative contributions to model output variability and uncertainty (U.S. EPA 2001b).

Short-Term Exposure – Repeated exposure by the oral, dermal, or inhalation route for more than 24 hours, up to 30 days.

Slope Factor – An upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime exposure to an agent. This estimate, usually expressed in units of proportion (of a population) affected per mg/kg/day, is generally reserved for use in the low-dose region of the dose-response relationship, i.e., for exposures corresponding to risks less than 1 in 100.

Source – The origin of an agent for the purposes of an exposure assessment.

Source-to-Dose Model – An approach where an environmental agent is followed from its source to the resulting dose.

Stakeholder – An interested party who is concerned with the decisions made about how a risk may be mitigated, avoided, reduced, or eliminated, and the communities that may be impacted by regulatory decisions.

Stressor – Any entity, stimulus, or condition that can modulate normal functions of the organism or induce an adverse response (e.g., agent, lack of food, drought).

Superfund – Federal authority, established by the *Comprehensive Environmental Response, Compensation, and Liability Act* (CERCLA) (U.S. 96th Congress, 1980) to respond directly to releases or threatened releases of hazardous substances that may endanger health or welfare.

Susceptibility – Increased likelihood of an adverse effect or an exposure, often discussed in terms of relationship to a factor, that can be used to describe a human subpopulation (e.g., lifestage, demographic feature, or genetic characteristic).

Susceptible Subgroups – May refer to lifestages (e.g., children or the elderly), or to other segments of the population (e.g., asthmatics, the immune-compromised, or the highly exposed). The term is likely to be chemical-specific, and may not be consistently defined in all cases.

Target Organ – The biological organ most adversely affected by exposure to a chemical, physical, or biological agent.

Toxicity – Deleterious or adverse biological effects elicited by a chemical, physical, or biological agent.

Toxicodynamic (TD) – The determination and quantification of the sequence of events at the cellular and molecular levels leading to a toxic response to an environmental agent (sometimes referred to as pharmacodynamics, also MOA.

Toxicokinetic (TK) – The determination and quantification of the time course of absorption, distribution, metabolism, and excretion of chemicals (sometimes referred to as pharmacokinetics).

Toxification – Metabolic conversion of a potentially toxic substance to a product that is more toxic.

Uncertainty – Uncertainty occurs because of a lack of knowledge. It is not the same as variability. For example, a risk assessor may be very certain that different people drink different amounts of water but may be uncertain about how much variability there is in water intakes within the population. Uncertainty can often be reduced by collecting more and better data, whereas variability is an inherent property of the population being evaluated. Variability can be better characterized with more data but it cannot be reduced or eliminated. Efforts to clearly distinguish between variability and uncertainty are important for both risk assessment and risk characterization.

Uncertainty Factor (UF) – One of several, generally 10-fold, default factors used in operationally deriving the RfD and RfC from experimental data. The factors are intended to account for
- variation in susceptibility among the members of the human population (i.e., interindividual or intraspecies variability)
- uncertainty in extrapolating experimental animal data to humans (i.e., interspecies uncertainty);
- uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure)
- uncertainty in extrapolating from a LOAEL rather than from a NOAEL and
- uncertainty associated with extrapolation when the database is incomplete.

Variability – Variability refers to true heterogeneity or diversity. For example, among a population that drinks water from the same source and with the same contaminant concentration, the risks from consuming the water may vary. This may be due to differences in exposure (i.e., different people drinking different amounts of water and having different body weights, different exposure frequencies, and different exposure durations) as well as differences in response (e.g., genetic differences in resistance to a chemical dose). Those inherent differences are referred to as variability. Differences among individuals in a population are referred to as *interindividual variability*; differences for one individual over time is referred to as *intraindividual variability*.

Vulnerability – A matrix of physical, chemical, biological, social, and cultural factors which result in certain communities and subpopulations being more susceptible to environmental toxins, being more exposed to toxins, or having compromised ability to cope with and/or recover from such exposure. Four types of vulnerability are considered with regard to a

lifestage approach: susceptibility or sensitivity, differential exposure, differential preparedness, and differential ability to recover (NEJAC, 2004).

Weight-of-Evidence (WOE) – An approach requiring a critical evaluation of the entire body of available data for consistency and biological plausibility. Potentially relevant studies are judged for quality and studies of high quality given much more weight than those of lower quality (see U.S. EPA, 2000b, pages 4-11-12).

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