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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
ADME	Absorption, distribution, metabolism, and elimination
ARE	Acute reference exposure
AUC	Area under the curve
BBDR	Biologically based dose-response
BMD	Benchmark dose
BMDL	Benchmark dose lower confidence level
C_{max}	Maximum concentration
CatReg	Categorical regression
CSF	Cancer slope factor
CYP	Cytochrome P450
DAF	Dosimetric adjustment factor
EHC	Environmental health criteria
EPA	U. S. Environmental Protection Agency
FQPA	Food Quality Protection Act
GFR	Glomerular filtration rate
HA	Health advisory
HEC	Human equivalent concentration
HED	Human equivalent dose
LOAEL	Lowest-observed-adverse-effect level
MOA	Mode of action
MRL	Minimal risk level
NOAEL	No-observed-adverse-effect level
PBTK	Physiologically based toxicokinetics
POD	Point of departure
RfC	Reference concentration
RfD	Reference dose
RfV	Reference value
SAR	Structure-activity relationships
TD	Toxicodynamics
TK	Toxicokinetics
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 Academy of Science released a watershed report on Pesticides in the diets of infants and children regarding evaluation of risk to environmental exposures (NRC, 1993). In addition to this report and in response to it, increased emphasis on protecting children from environmental exposures has evolved due to mounting scientific evidence to support the vulnerability of the developing fetus and child as well as legislative and administrative mandates. 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 requiring a focus on the evaluation of children's exposures and toxicities in the context of risk assessment. In 1997, Presidential Executive Order 13045, *Protection of Children from Environmental Health Risks and Safety Risks* (April, 1997), gave further emphasis to the need for establishing potential risks from childhood environmental exposures. *Strategy for Research on Environmental Risks to Children* was published by EPA in 2000 (U.S. EPA, 2000d).

EPA risk assessment guidelines relevant to children's health issues had been published (U.S. EPA, 1991,1996; 1998b), and other guidelines (U.S. EPA, 2005b, 2005c), policies, and recommendations were under development (U.S. EPA, 2002a; U.S. EPA, 2002b; U.S. EPA, 2003b). Implementation of the FQPA and SDWA amendments required additional development of guidance and policy for protecting children's health, particularly the application of the FQPA 10-fold safety factor (U.S. EPA, 2002c). Thus, there are a number of guidelines and policies related to children's health, but there is 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, but much has happened since the draft was completed. This framework

document builds on that report and other drivers 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 organized by the International Life Sciences Institute Risk Science Institute and held in Stowe, VT, July 30–August 2, 2001. The report of that workshop (ILSI, 2003) and subsequent publications (Olin & Sonawane, 2003; Daston et al. 2004; Landrigan et al., 2004; Ginsberg et al., 2004c; Morford et al., 2004) proposed a framework for children's health risk assessment and laid out a number of issues of concern. The current framework builds on the dedicated 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 or practice of pediatrics or involving pediatric issues within the FDA. Assessment of risks and benefits to children is conducted in compliance with the Pediatric Research Equity Act (U.S. FDA, 2003b), 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 guidance documents 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, 2003a), addresses considerations on the evaluation of pharmaceuticals in juveniles, one of the life stages discussed in this Framework.

Additionally, the International Programme for Chemical Safety of the World Health Organization is in the process of developing an Environmental Health Criteria (EHC) document entitled *Principles for Evaluating Health Risks Associated with Chemical Exposures to Children*. When completed, the EHC document will serve as useful background information for utilizing this framework.

Finally, EPA's Risk Assessment Forum has been working for several years to harmonize approaches to 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] *Framework for Children's Health Risk Assessment* was the previous title of this document.

1. EXECUTIVE SUMMARY

The purpose of this document is to provide *(1)* a single resource for information on the assessment of health risks to children as a result of exposures of environmental agents, and *(2)* an overarching framework for a more complete assessment of health risks to children from exposures of environmental agents within EPA's risk assessment paradigm, which examines the impact of potential exposures during all stages of development, while emphasizing the iterative nature of the analysis phase with a multidisciplinary team. In addition to outlining the risk assessment process, 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.

The term "children" as used in this document includes the stages of development from conception to adulthood. The assessment of health risks to children from environmental exposure, or "children's exposure" as used throughout this document, includes exposure before conception, as well as during the developmental life stages from conception through adolescence. Health risks may be detected during the same life stage as when the exposure occurred or they may not become apparent until much later in life. Life stages are defined in this document as temporal stages (or intervals) of life that have distinct anatomical, physiological, and behavioral or functional characteristics that contribute to potential differences in vulnerability to environmental exposures. A life stage approach to risk assessment considers the timeframe or life stage of exposure and outcome when evaluating the data. A life stage approach for evaluation of risks to children takes into account all relevant periods of exposure, and explicitly considers where data do and do not exist for both exposure and health outcomes. It focuses on considerations of early life stage exposure, and subsequent outcomes, which may not be expressed until later life stages. Information on mode(s) of action and pharmacokinetics that may inform life stages are another main emphasis of this approach. Risk assessment using a life stage 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 to children and other subpopulations.

The added value of using a life stage approach to risk assessment is a more comprehensive evaluation of the potential for vulnerability of various populations at different life

stages. The approach outlined here encourages evaluation of the potential for toxicity during all developmental life stages, based on knowledge of external exposure, critical windows of development for different organ systems, modes of action (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 EPA cancer guidelines (U.S. EPA, 2005b, 2005c) but is extended to the evaluation all outcomes.

It is important that one needs to consider whether anything is known about developmental life stages that would indicate particular vulnerability and incorporate that information in the assessment. This document also addresses the difficult issue of integrating toxicity data and exposure information, which is especially challenging when data are limited for particular time periods during pregnancy and early childhood development.

The conceptual framework used in this document follows the basic framework developed for other areas of risk assessment 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 children's health risk assessment are also discussed. In particular, guidance is lacking for life stage-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 outcomes for application to risk assessments for various durations of exposure has not been defined, even though this issue is considered in many of the risk assessments currently being generated across EPA.

2. INTRODUCTION, PURPOSE, AND SCOPE

The purpose of this document is to provide *(1)* a central resource of the information available for assessing risks as a result of environmental exposures to children, and *(2)* to provide an overarching framework for assessing health risks that examines the impact of potential environmental exposures during all stages of development. The term "children" as used in this document includes the stages of development from conception through adolescence to adulthood. The assessment of health risks to children from environmental exposure, or "children's exposure," includes exposure to either parent before conception as well as during the developmental life stages from conception through adolescence. Health risks may be detected during the same life stage as when the exposure occurred or they may not become apparent until later in life.

The major question to be addressed by use of this document is: What is the risk of environmental exposure to children? This framework outlines the essential phases in making judgments about the risks of children's exposure to environmental agents, 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 children's exposures can be incorporated into the larger 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 risks to children as a result of exposure, existing sources for more detailed information 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.

The conceptual framework used in this document follows the basic framework developed for other areas of risk assessment (e.g., *Guidance on Cumulative Risk Assessment*, U.S. EPA, 1997a; *Guidelines for Ecological Risk Assessment*, U.S. EPA, 1998a) and includes problem formulation, analysis, and risk characterization as the three major phases in the process. Figure 2-1 shows this general health risk assessment framework.

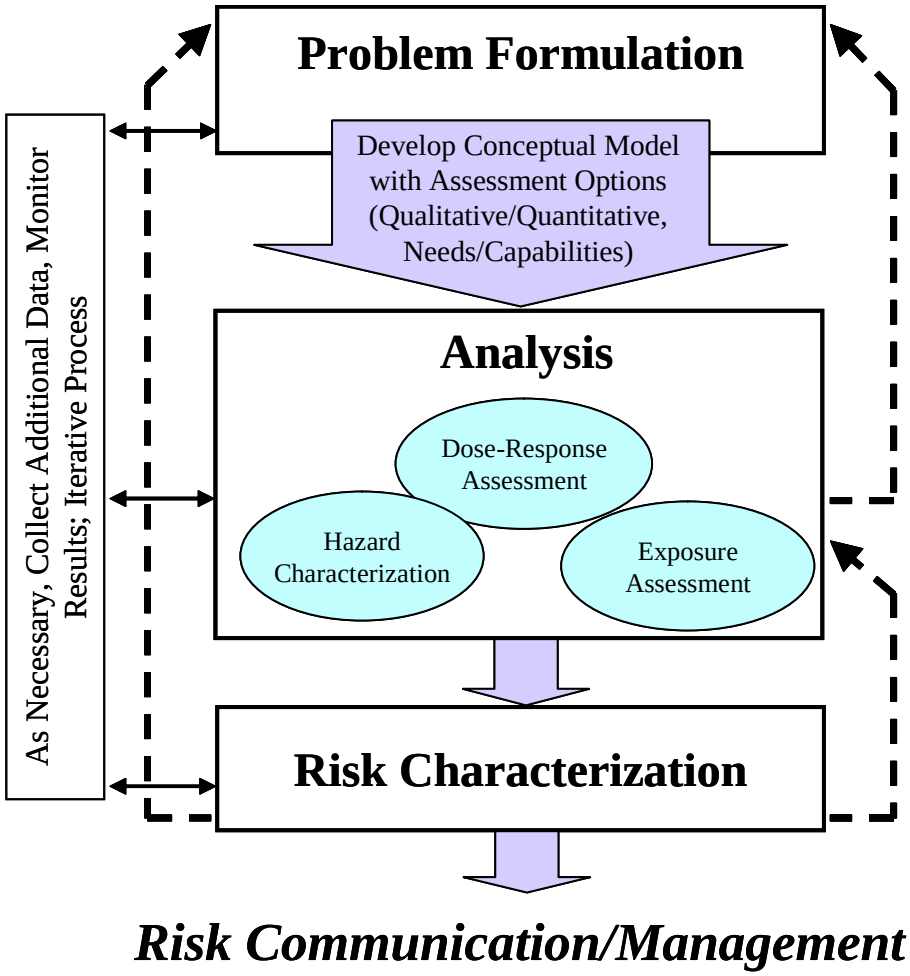


Figure 2-1. General health risk assessment framework. This general health risk assessment framework is adapted from *Guidance on Cumulative Risk Assessment* (U.S. EPA, 1997a) and includes three phases also identified in *Guidelines for Ecological Risk Assessment* (U.S. EPA, 1998a): problem formulation, analysis, and risk characterization.

The outline for this document adopts the general framework for health risk assessment with a focus on life stage analysis (Figure 2-2, adapted from the framework in Daston et al. (2004), and, in each phase of the process raises questions to consider in assessing health risks to children from environmental exposure. This document incorporates information from relevant risk assessment guidelines and other reports while focusing on susceptibility, both inherent and acquired, at different life stages, as well as the potential for greater exposure of environmental agents to children than adults.

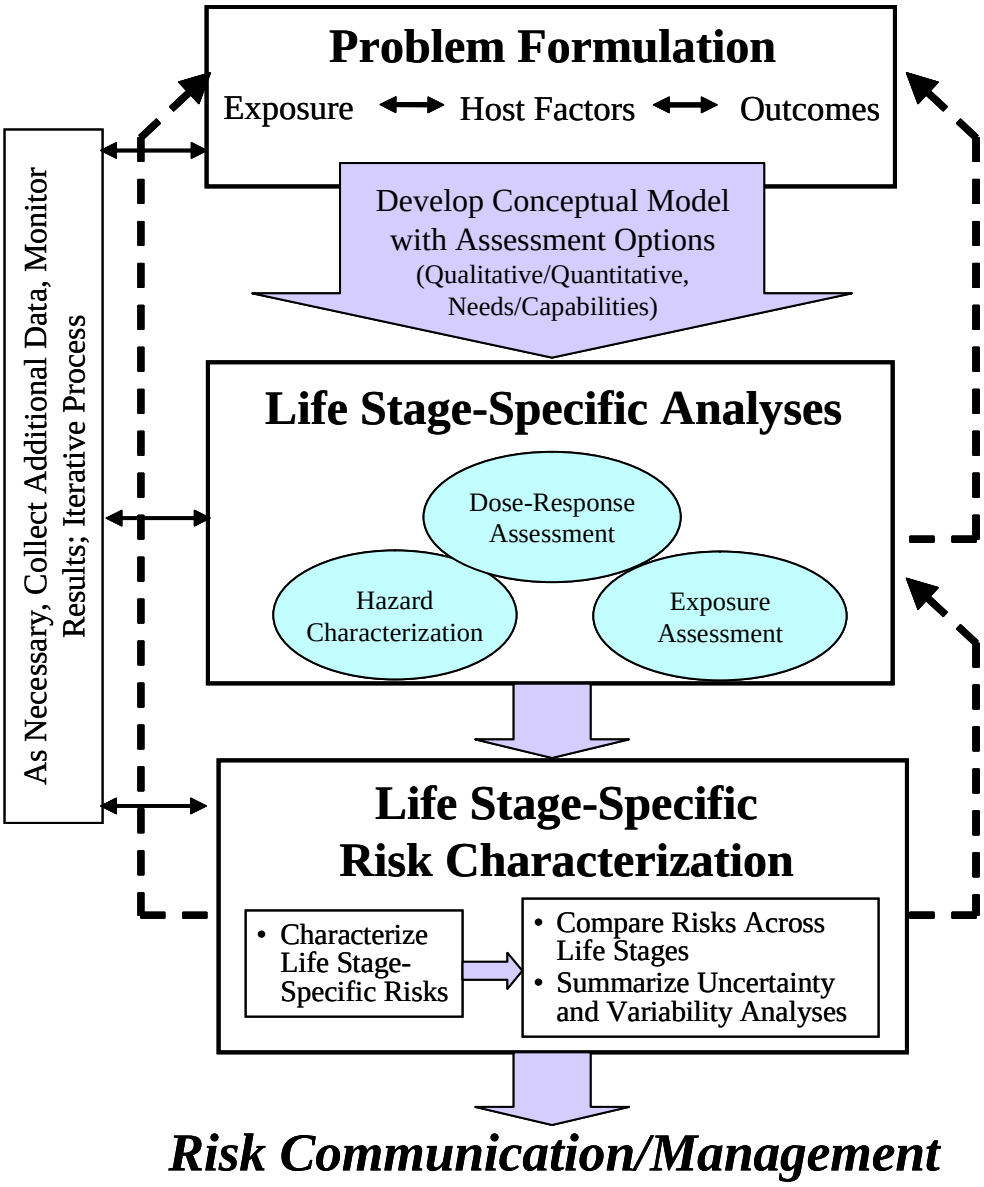


Figure 2-2. Children's health risk assessment framework. This children's risk assessment framework diagram expands on the theme presented in Figure 2-1, with increased emphasis on life stage-specific evaluations during problem formulation, analysis, and risk characterization. (Source: Adapted from Olin & Sonawane, 2003.)

Assessing health risks to children as a result of environmental exposure to children includes the consideration of risk from exposure before conception, during the prenatal period, and through childhood to adolescence (Figure 2-3). Life stages 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

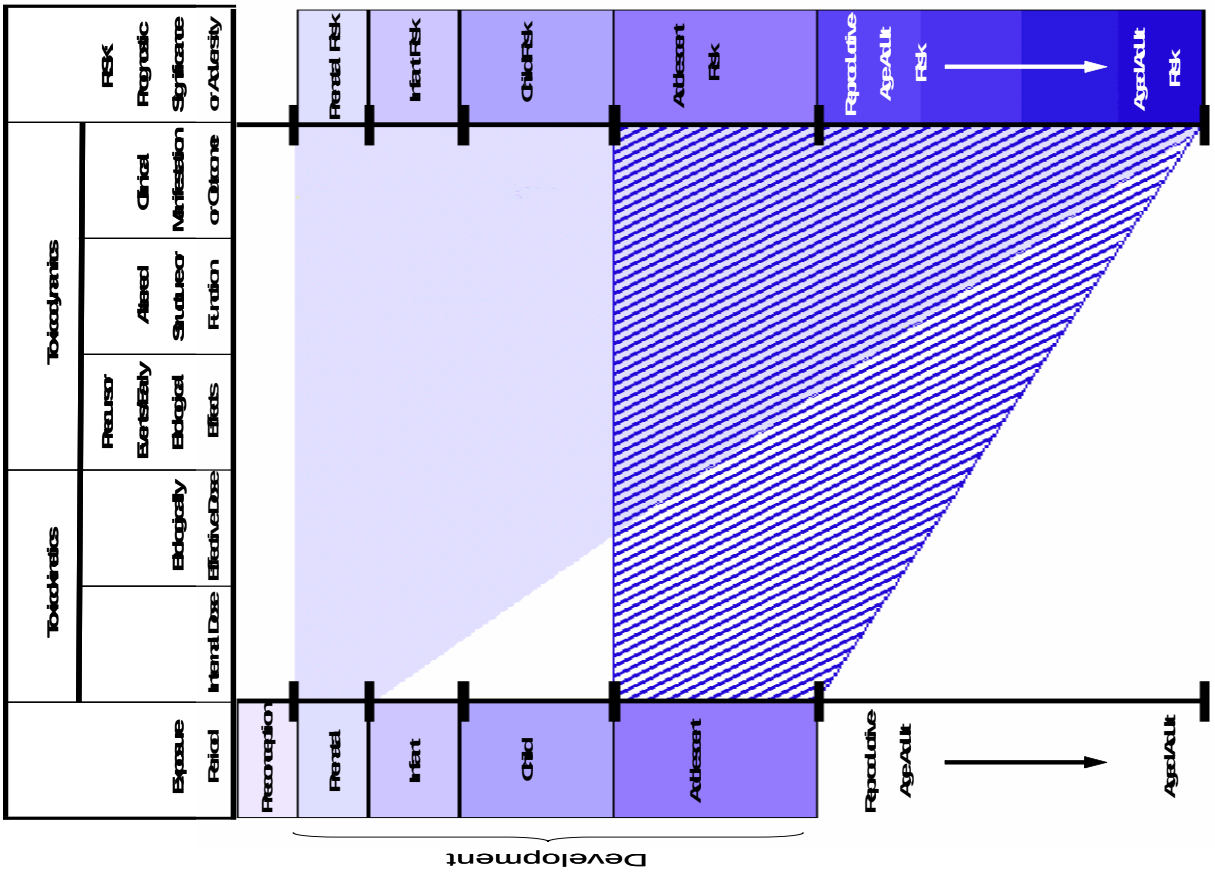


Figure 2-3. Life stages of outcomes after developmental exposure. This figure illustrates the different life stages during which developmental exposures may occur (before conception through adolescence). Exposure (shown on the left side of the figure) during a given life stage may result in outcomes observed during that same stage or later in life (shown on the right side of the figure). For illustrative purposes, the outcomes associated with exposure during two periods, prenatal and adolescence, correspond to the highlighted and hatched regions, respectively. Broad exposure intervals, e.g., "child," are shown here for illustration; divisions between all life stages are not precise. There is some reproductive age overlap between the adolescent and the adult periods.

exposures.[2] The life stages from conception through adolescence comprise the period of development; outcomes may occur during that same life stage or later in life. Neither the outcomes nor the risks from these exposures will necessarily be the same. Rather, the outcomes will depend on the underlying developmental processes that determine susceptibility at the time

[2] *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; the *toddler* stage is from the first birthday through the third birthday; *childhood* encompasses all early life stages from birth through *adolescence*, 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 of age. Divisions between all life stages are not precise (U.S. EPA 2001c, U.S. EPA, 2002b, Table 3-1).

of exposure. A life stage approach for evaluation of 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 expression and is predicated on considerations of mode(s) of action considerations for all life stages of exposures. Risk assessments may require finer definition of exposure intervals than those shown in the figure because of rapid changes during development, even within a life stage. 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. In addition, areas are identified where further guidance is needed, as are areas in need of research to support guidance. 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 document 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 state of the science for assessing risk to children. It is not intended to be proscriptive. The intended users of this approach are risk assessors involved in hazard characterization, dose response analysis, and exposure characterization who consider children's risk to environmental exposures. The central focus of this framework is the developing embryo, fetus, and child, thus extending and expanding the approach in *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991). 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. Because children are not a unique population but rather that all individuals pass through a series of life stages, this is considered a public health-oriented approach.

The added value of using a life stage approach to assess risks to children from environmental exposure is a comprehensive evaluation of the potential for vulnerability of

various populations at different life stages. In contrast, assessments often rely only on the available data, which can be limited to data for adults, and they do not necessarily account for the lack of data at other life stages. The approach outlined here encourages evaluation of the potential for toxicity during all developmental life stages, 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 the course of developing an assessment, the lack of data for certain life stages is not meant to imply greater uncertainty in the assessment of risk to children. Rather, the intent is to consider whether anything is known about life stages 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 for assessing risks. This integration is especially challenging because of data limitations for particular periods during pregnancy and early childhood development. A product of using this framework will be risk characterizations that are more transparent and scientifically justifiable with documentation of data gaps and data needs for children's risk.

The approach outlined here encourages evaluation of the potential for toxicity during all developmental life stages, 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. MOA is defined in this framework as the[0] 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, 2005b, 2005c). Both toxicodynamic and toxicokinetic steps are part of the mechanism and mode of action leading to the toxic response (Clewell et al., 2002a; Andersen et al., 2000). As stated in the latest cancer guidelines, "MOA is contrasted with mechanism of action, which implies a more detailed understanding and description of events, often at the molecular level" (U.S. EPA, 2005b, 2005c).

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

3. 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 step 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 assessment of any life stage of exposure (Figure 3-1). However, some of the specific considerations will be different in a risk assessment for childhood exposures. This section focuses primarily on the considerations for assessments of childhood exposures.

Problem formulation includes an initial characterization of exposures and outcomes during all developmental life stages, a planning and scoping phase, and the development of two products: a conceptual model and an analysis plan (Figure 3-1).

3.1. PLANNING AND SCOPING

In the planning and scoping phase, the assessment goals, breadth, and focus are established and regulatory and policy factors are identified. These steps include defining and identifying the purpose, scope, participants, approaches, resources, and relevant past assessments available. The extent of the risk assessments can be site specific, chemical specific, receptor based or broader in scope. In an assessment with a focused scope, potential outcomes for specific life stages thought to be at risk are analyzed; in the broader-scope assessment, each life stage is considered in the analysis steps of the assessment. Some of the questions that may need to be considered are:

- Will the assessment consider, for example, exposure at all developmental periods (from preconception through adolescence into adulthood) in the general population and all possible sources, media, pathways and routes of exposure (aggregate and cumulative), or is it confined to specific scenarios such as children living near a specific Superfund site and potentially exposed via air, soil, and groundwater?

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

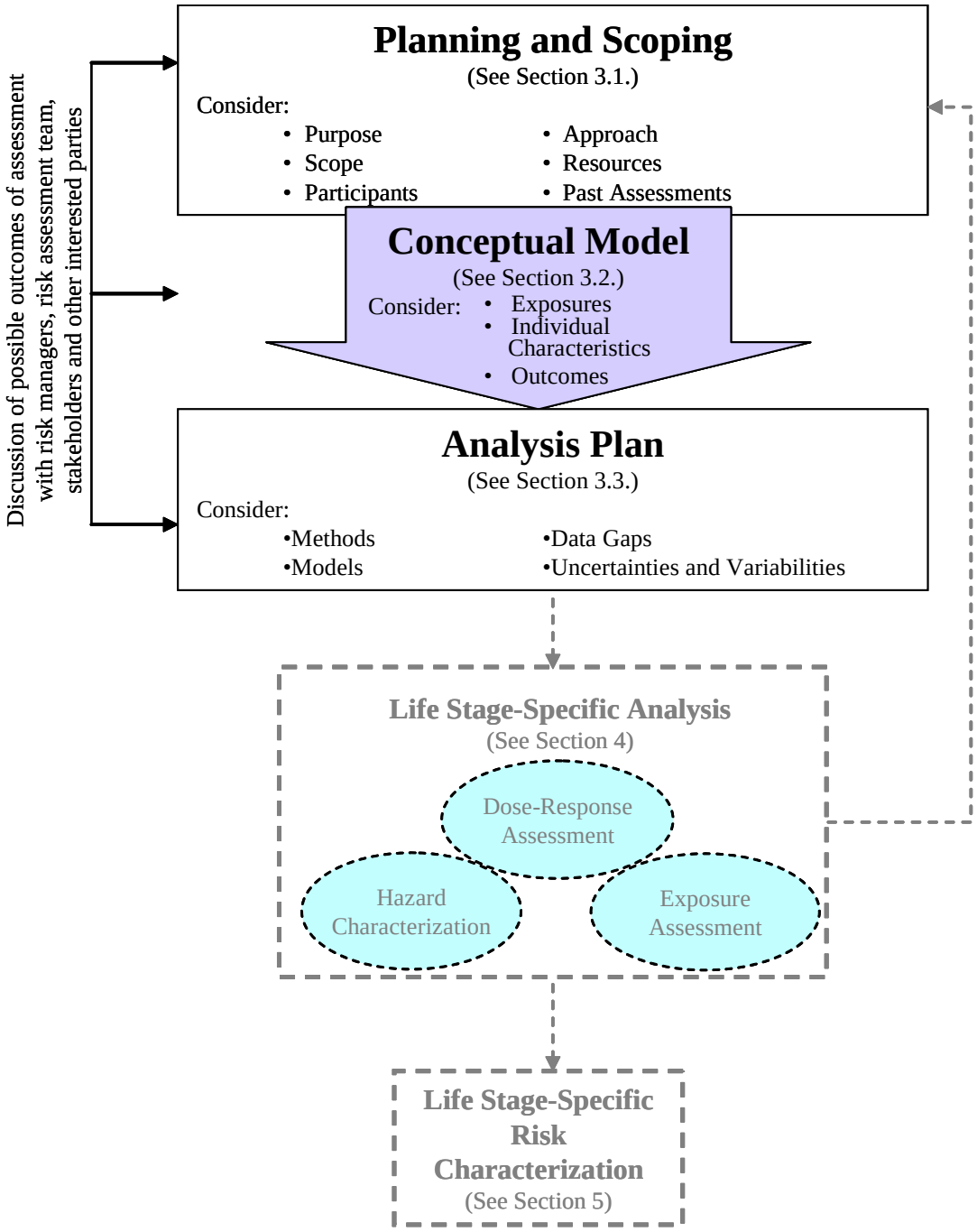


Figure 3-1. Flow diagram for life stage-specific problem formulation. This figure illustrates the flow of information and analysis that comprises problem formulation. The problem formulation phase establishes the context of the risk assessment and feeds into the life stage-specific analysis phase and ultimately to risk characterization (dotted line boxes). The problem formulation results in two products. First, a conceptual model is developed from both the planning and the scoping phases, and the consideration of exposures (e.g., sources, receptors, stressors, pathways, individual characteristics) and outcomes. Second, an analysis plan 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 assessment, and exposure assessment. Source: Adapted from U.S. EPA, 2003a, Figure 1-3.

In this phase, a clear purpose of the assessment is defined in order to guide the risk assessment strategy. The scope sets the parameters of the assessment, allowing for decisions to include or exclude various elements.

- Why is it being done?
- How will it be used?
- What is the public health concern?
- What is (are) the risk question(s) being asked?
- What is (are) the regulatory driver(s)?

The participants who have information, expertise, or a stake in the assessment process and outcome(s) of the assessment are identified. Risk assessors, risk managers, and stakeholders (e.g., impacted community, non governmental organizations) are involved in the process (U.S. EPA, 2001b). 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, as well as those who may be affected by regulatory decisions. Those participating in the problem formulation will depend on the problem being addressed. Guidelines for stakeholder involvement are provided in *Framework for Cumulative Risk Assessment* (U.S. EPA, 2003a, p. 21) and are based on the recommendations in *Science and Judgment in Risk Assessment* (NRC, 1994) and the *Presidential/Commission on Risk Assessment and Risk Management* (NAS, 1997).

The approaches, such as methods and models, for developing a conceptual model and analysis plan are identified and selected. Identifying resources that will be required to achieve assessment goals within the timeframe of the assessment is necessary. Finally, identifying past assessments that relate to the purpose and scope of the assessment may assist the process with existing tools, methods, or models.

Risk assessments are often conducted within the context of a regulatory requirement, a community need, a health concern, or some other driving force (U.S. EPA, 2003a) and require varying levels of scope or depth (U.S. EPA 2005b, Section 1.2.2). During planning and scoping, the risk assessment team (which includes the risk planning team; epidemiologists; public health specialists; toxicologists, including disciplinary specialist; 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, to develop the rationale, scope, and relevant outputs for the risk assessment and characterization.

This phase of problem formulation involves a qualitative screening evaluation of existing information to scope the assessment and identifies whether children might have a greater potential for higher exposures or greater intrinsic susceptibility. The evaluation includes an examination of the quality and quantity of the available data on exposure and outcomes. More detailed evaluations may or may not be necessary or 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 concern about the public health outcome), a more detailed approach can be employed to address essential questions needed for the exposure and health effects characterization.

Children's health risk assessment requires specialized expertise and understanding of critical windows of exposure and optimum timing for evaluation of outcomes. For example, experts in reproductive and developmental toxicology and epidemiology, neurotoxicology, pulmonary toxicology, children's behavior, and exposure assessment may be needed, depending on the particular problem or agent(s) of concern. It is important that all risk assessors have a basic understanding of windows of exposure and timing for evaluation because these concepts can provide a common framework for both the exposure assessment and the hazard characterization components of the analysis phase.

There may be regulatory requirements that have to be considered in this process. For example, there may be judicial and societal considerations that may influence the timing and breadth of the assessment. 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 required to satisfy such requirements.

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, 2000e, 2003e, 2005f). 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 also requires dialogue between risk assessors and economists.

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 goal of identifying relevant stressors, sources, pathways (including exposure media and routes), receptors (exposed individual or population), and outcomes, along with the relationships among them.

Problem formulation results in a qualitative characterization of hazard and exposure for specific life stages. The outcome is the accumulation of the information needed to develop a conceptual model (Figure 3-2) that aids the segue from the problem formulation stage to the analysis phase. The conceptual model forms the basis for the life stage-specific analysis. It can be presented as a diagram, a flow chart, or a narrative description of the predicted key relationships.

These key relationships include the exposures, host factors, and the biological effects. They are informed by the initial identification of exposure scenarios, the life stage of exposure, the optimum times for evaluation of outcomes to be covered, and the identified characteristics and toxicological outcomes of the chemical(s) that may contribute to children's risk.

3.2.1. Exposure Considerations

The approach is to perform a preliminary examination of the data to determine the life stages likely to be affected, given the properties of the environmental agent(s), possible sources and pathways of exposure, and the defined scope of the assessment. This involves a qualitative characterization of the sources, nature, magnitude, duration and pattern of exposures to parents or children, as appropriate, including the potential for dietary, drinking water, soil and air exposures, and other sources (e.g., pharmaceuticals) (U.S. EPA, 1992, 2002a). An important issue to consider is whether all life stages are at the same risk from exposure (e.g., from air toxicants, water contaminants), or whether a specific developmental life stage is more vulnerable

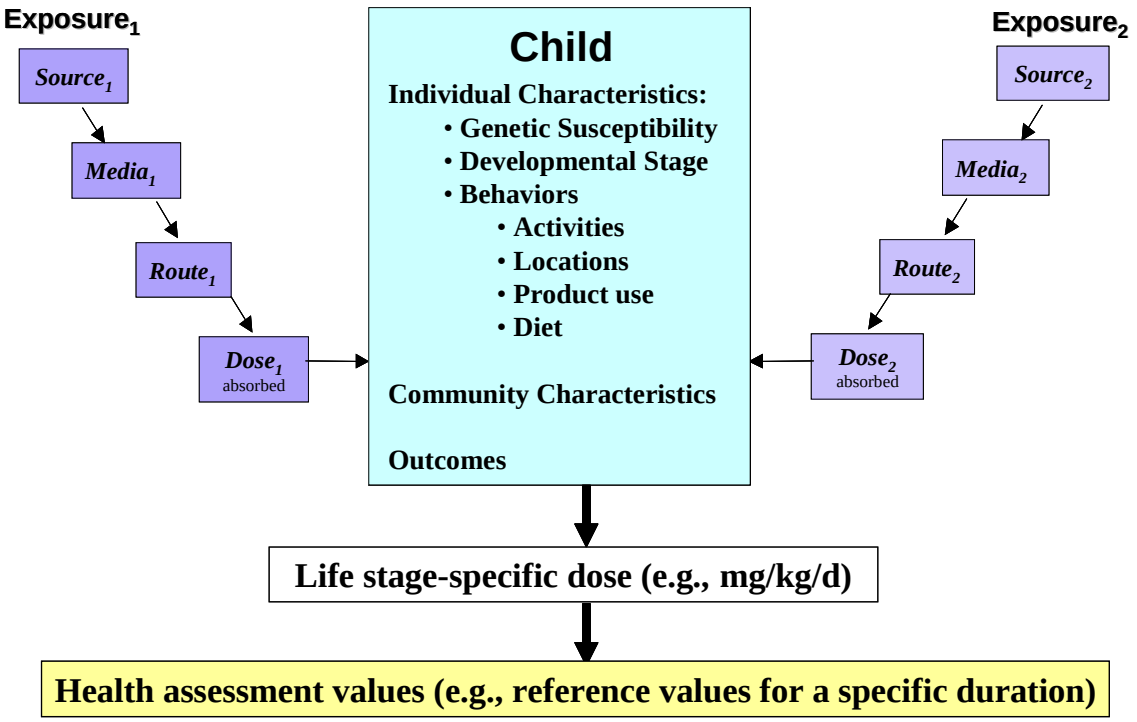


Figure 3-2. Conceptual Model for Problem. This figure shows an example of a conceptual model resulting from the problem formulation planning and scoping phase. Sources, media, routes, dose, pathways, individual characteristics, and outcomes are presented. The types of information to consider in developing a conceptual model include exposure, individual characteristics, and outcomes (Figure 3-1). The following three subsections provide an approach to a preliminary evaluation of the available data to help define the conceptual model and aid in the development of a problem-driven analysis plan.

because of higher exposures or intrinsic susceptibility. A given product's or compound's properties, as well as its commercial uses and sources of exposure, provide qualitative information on where it is expected to be found in exposure media.

Information on exposure pathways and a qualitative understanding of activity patterns (patterns of exposure) can be used to identify potentially highly exposed life stages. Some considerations specific to children include *1)* exposure media (e.g., breast milk, indoor air; see Section 4.3.4.2), *2)* behaviors, activities, and locations that are a function of age/developmental stage (e.g., mouthing, crawling; see Section 4.3.4.4), *3)* individual and community characteristics (e.g., SES, cultural practices; see Section 4.3.4.3), and *4)* physical environment (e.g., climate; see Section 4.3.4.1). Qualitative information should be used to identify all potential sources, pathways (exposure media and routes), and scenarios (population, time frames, locations, and activities).

3.2.2. Outcome Considerations

In this screening approach a preliminary identification of toxic effects is preformed, including kinetic and dynamic profiles. Some questions to consider are:

- What do we know about the chemical being evaluated that may be important for considering age-specific risk?
- Does the chemical cause known organ-specific toxicity?
- Which organs are targeted, and how are these organs differentially susceptible during development?
- What are the background rates for outcomes of concern in the general population?
- What are the specific time periods of concern?
- Are there toxicokinetic (e.g., metabolic activation/conjugation) or toxicodynamics considerations that may make the chemical more or less toxic during certain developmental life stages?

3.2.3. Integration of Exposure Considerations and Biological Effects Considerations

The concepts of timing and dosimetry are incorporated as unifying factors for both exposure and hazard components of the analysis.

- How do sources, nature, magnitude, and patterns and pathways of exposure influence target outcomes?
- How does dosimetry impact the temporal resolution required for exposure assessment?
- Based on the fate of the product or compound being evaluated, are we assessing hazard of the compound(s) to which children are actually exposed?
- What MOAs are being considered for relevant child health outcomes?
- What dose metrics (e.g., AUC or C_{max}) are being considered for child related assessments?

3.3. ANALYSIS PLAN

The analysis plan should identify the methods, models, critical data gaps, major uncertainties, and key assumptions that need to be considered as the problem-driven assessment moves forward to more in-depth analyses. The analysis plan is a working

outline that provides the rationale for the expertise, time, and resources required to complete the assessment.

A database inventory may be useful for identifying data gaps (Figure 3-3). Negotiation of consensus among the relevant risk managers may be needed on the conceptual model and analysis plan, including the possible outputs of the assessment. This exercise can facilitate identification of strengths and weaknesses in the database, especially with regard to life stage assessment.

Planning and scoping, the conceptual model, and the analysis plan are then used in the life stage-specific analysis, which comprises hazard characterization, dose-response assessment, and exposure assessment. Further scoping may be considered in each of the three analysis phases, thus leading to a further refinement of the conceptual model and analysis plan.

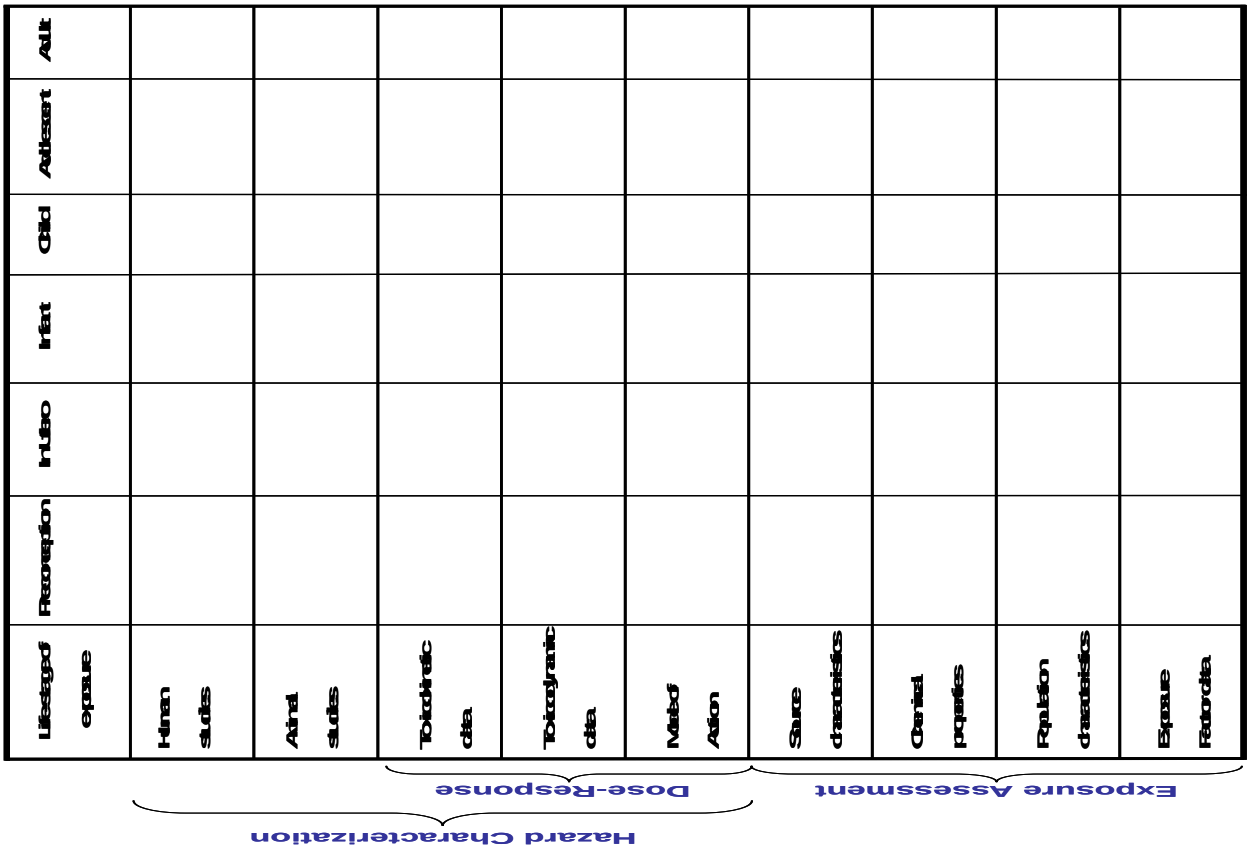


Figure 3-3. Life stage-specific database inventory sheet. This table presents an example of a database inventory method. Types of information are described in the left-hand column, and life stages of exposure are shown in the top row. After assessing the available information on life stages of exposure, the assessor can note whether there are the different types of information for each life stage. For example, are there human studies assessing outcomes after in utero exposure?

4. LIFE STAGE-SPECIFIC ANALYSIS

The life stage-specific analysis includes hazard characterization, dose-response assessment, and exposure assessment phases. In these phases, data are analyzed, both qualitatively and quantitatively. Iterations among all three components are necessary for communication among the team members and stakeholders, as well as to refine the focus on the key assessment questions identified in the problem formulation phase (Figure 3-1). For children's health risk assessment, data on outcomes after exposure during life stages of greatest susceptibility (critical windows) are key to the evaluation of hazard, dose, and exposure. Assessing the data by life stage of exposure and outcome is necessary. This includes the identification of data gaps for particular life stages of exposure and, data that may identify critical windows of exposure. Mode of action information based on toxicokinetic and toxicodynamic data may inform the life stage specific analysis (Figure 4-1). The next three sections discuss the factors important in each part of the analysis phase and provide information to guide the assessor through the process.

Dose-response assessment for health risk assessment of children's exposures must consider both timing and dosimetry; and links the characterization of the exposure with potential health effects. In order to link exposures and outcomes appropriately, an iterative process comparing duration of exposure and dosimetry by life stage of development is recommended. Integrating hazard and exposure data is important for a robust risk characterization, the final phase in the risk assessment process. The integration process is discussed further in Section 4.3.4.

4.1. HAZARD CHARACTERIZATION

4.1.1. Introduction

Hazard characterization is the risk assessment phase in which the data are evaluated for potential adverse health effects. It includes the identification of any outcomes associated with exposure and dose. The primary purpose of hazard characterization for children's health risk assessment is the evaluation of the potential for life stage-specific health outcomes after exposure during preconception or developmental stages, taking into consideration toxicokinetic (TK), toxicodynamic (TD), and dose-response information. Information derived from both human data and animal toxicology studies are evaluated in this analysis phase. Additionally,

information about differences and similarities in experimental animal models versus humans regarding life stage-specific TK and TD should be considered in the evaluation. More specific information on hazard characterization for developmental life stage exposures can be found in the existing 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, 2005c).

Figure 4-2 illustrates a detailed approach to characterizing hazard to children from environmental exposures. This framework is based on the use of a life stage approach (Figure 2-3), which evaluates data according to the life stage for exposure, outcome, and all intervening steps (e.g., TK, TD). This approach focuses on exposures prior to conception and during development (i.e., conception to young adulthood), but outcomes at any life stage up to and including adulthood are considered (i.e., conception to aged adult). It provides a temporal context within which to evaluate data for risk assessment. Thus, the initial evaluation of data for a chemical or mixture considers what information is available (and not available, i.e., data gaps) for different life stages and what the data indicate in terms of life stage-specific susceptibilities.

Figure 4-2 presents a flow diagram for life stage-specific hazard characterization. In the scoping step of hazard characterization, information on life stage differences in exposure and susceptibility is described, assembled by life stage, and synthesized in the hazard characterization segment of the assessment (Section 4.1.2). Following the scoping step, there are three major steps in the data evaluation process. In the first step, a detailed qualitative evaluation of each study is developed (Section 4.1.3). In the second step, the database is synthesized from the individual study evaluations, and the quality and quantity (i.e., the comprehensiveness) are characterized (Section 4.1.4). This step utilizes a weight of evidence (WOE) approach. In the final step (Section 4.1.5), the life stage-specific hazard characterization is summarized. A scientific rationale for the selection of relevant outcomes and susceptible life stages is developed based upon the data. The selected outcomes and susceptible life stages are further evaluated subsequently in the dose-response assessment phase. Finally, a comprehensive life stage-specific risk characterization is developed that requires iterative input among the dose-response, exposure, and hazard characterization assessment teams.

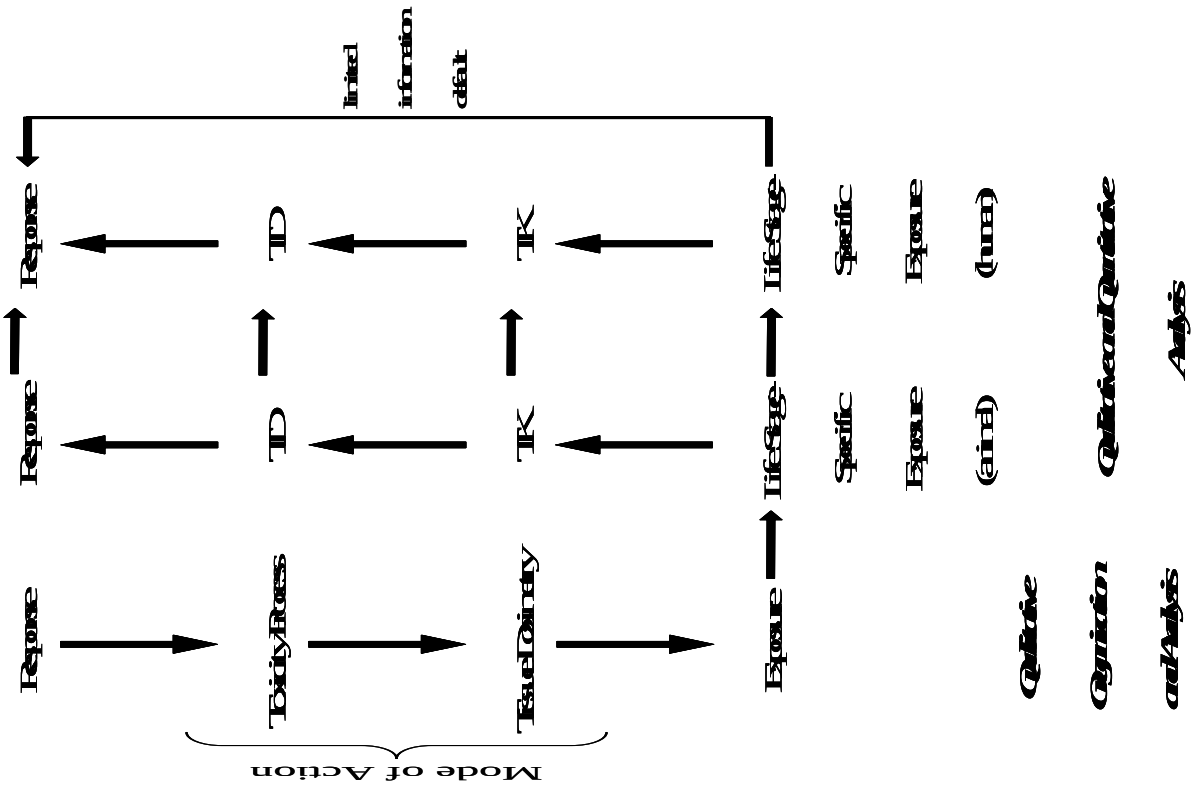


Figure 4-1. Framework for life stage-specific analysis with animal and human data. *Qualitative Organization and Analysis* represents the overall structure of the analysis phase of risk assessment, whereby observable responses are related to an exposure dose in which the intervening processes are known or unknown. *Qualitative and Quantitative Analysis* of sufficient data can predict response from exposure, informed by data on tissue dosimetry toxicokinetics (TK) and toxicity process toxicodynamics (TD). In instances where there is no mechanistic information (far right-hand side), animal dose-response data can be utilized and traditional default methods applied. Although much of the intervening information is often absent in humans, data from animal species can be used in a parallelogram approach to predict the various portions of the *Qualitative and Quantitative Analysis*. With TK data, dose metrics can be used to predict the overt response, or in data-rich settings the dose metric can be used to predict a TD event that can subsequently predict the overt response. As depicted in this figure, life stage-specific data in animals and humans is preferable, although in its absence, adult animal and human data may be useful as long as appropriate intraspecies life stage considerations and extrapolations are made. With certain analytical tools (e.g., physiologically based toxicokinetic models), tissue dosimetry information can be used to estimate the exposure or applied dose. In such instances, exposure analysis can inform selection of the most appropriate dose-response model(s) by providing information on to the relevant exposure levels at various life stages.

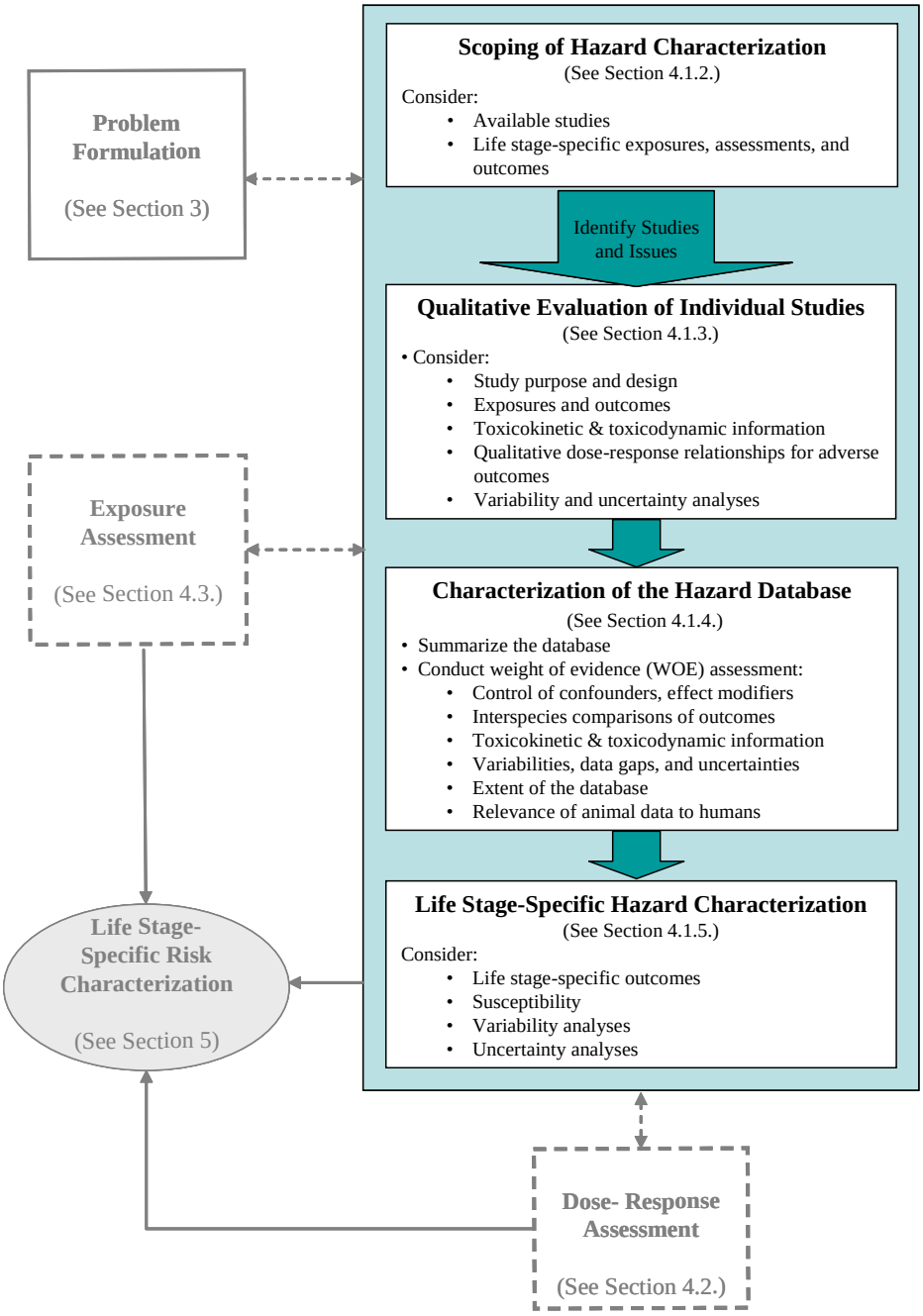


Figure 4-2. Flow diagram for life stage specific hazard characterization. This figure illustrates the flow of information and analysis that make up hazard characterization. Problem formulation establishes the context of the risk assessment and feeds into a hazard scoping process to identify the information that will be relevant for the hazard characterization phase. The three major steps in hazard characterization include the evaluation of individual studies, a weight of evidence assessment of the hazard database, and a full characterization of the hazard. For the assessment of risks to children, each phase of the process focuses on life stage-specific considerations. During the evaluation of hazard, repeated iterations (illustrated by dashed arrows) represent points when information is exchanged with other phases and may identify the need to collect more data or conduct more detailed analyses. Further refinement of the problem formulation or approach may also occur at these steps. As illustrated by the solid arrows, hazard characterization, dose-response assessment, and exposure assessment contribute to the risk characterization.

During each step, it is important to consider whether the information and conclusions address the overall goals of the assessment that were defined in the problem formulation phase. Each of these steps is described in subsequent sections, and questions that can help guide the life stage-specific hazard characterization process are presented in Appendix 1. The questions in Appendix 1 cover considerations for both human data and animal studies.

4.1.2. Scoping of Hazard Characterization

The refinement of the conceptual model during the hazard characterization focuses on the identification and evaluation of all human and animal toxicology data on outcomes resulting from preconception or developmental life stage exposures. The scoping exercise includes identifying studies for evaluation and determining the types of data available. The evaluation process considers life stage-specific information (pertaining to both the time of exposures and outcomes) and issues within the overall context of the risk assessment in order to focus on risks to children's health. Primary to this process is the identification of studies that assess outcomes after exposures within specific life stages, including preconception. The objectives and scope of the risk assessment, as identified in the problem formulation phase, provide structure and focus for this scoping step of hazard characterization. The culmination of hazard scoping is the identification of individual studies and issues to evaluate in greater detail.

4.1.3. Qualitative Evaluation of Individual Studies

The basis of the hazard evaluation process is a thorough examination of all published human and animal studies identified in the scoping phase. A thorough qualitative evaluation of each human and animal study includes, to the greatest extent possible, a complete description, an assessment of the data quality, and a determination of sufficiency of data for hazard characterization (Figure 4-3). To assess study quality, the adequacy of the methods and results must be fully characterized. In addition, it is be helpful to establish a basis or criteria for confidence in the evaluation and interpretation of the study findings. This phase, as implemented for each individual study, will contribute to the overall determination of the adequacy, strength, and completeness of the database for the characterization of hazard across life stages. After qualitative evaluation, the assessor should be able to identify the major strengths and weaknesses of the human and experimental animal database.

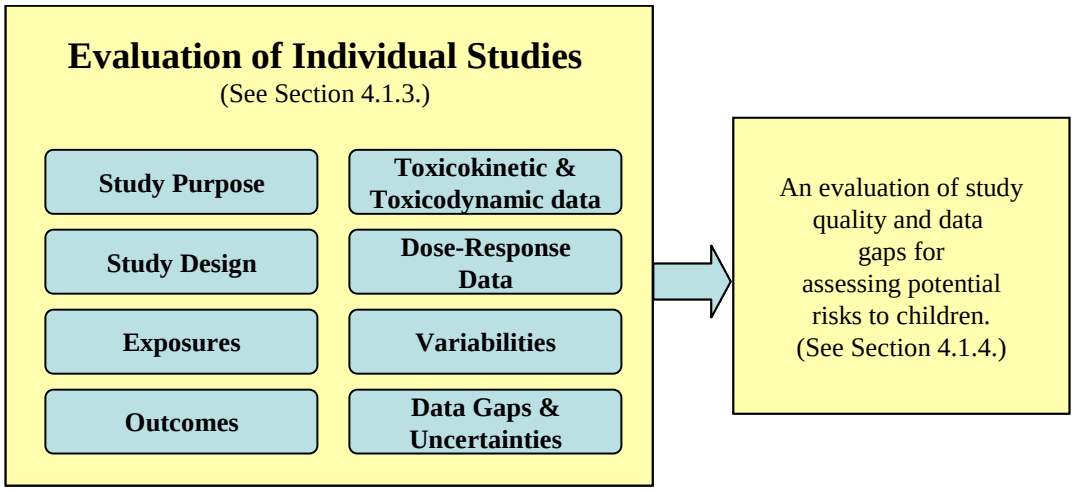


Figure 4-3. Hazard characterization Step 1: Evaluate individual studies with exposures during developmental life stages (including preconception). Following identification of studies with preconception or developmental life stage exposures and developmental or adult outcomes (i.e., hazard scoping), the first step in the analysis of hazard is an evaluation of each individual study, focusing on the details of study conduct, content, and outcomes. This step of the life stage-specific hazard characterization emphasizes a description of the timing of exposure and outcome. The resulting evaluation of study quality and data adequacy for assessing potential risks to children provides a firm basis for the life stage-specific hazard characterization process.

4.1.3.1. *Study Purpose*

Characterizing the intent or purpose of each study is necessary to focus the evaluation of the study and to assess the adequacy of the study to address issues by life stages. For example, the study may be conducted in response to general risk evaluation issues or as a result of a specific public health concern. The purpose of the study can range from hypothesis generation to hypothesis testing.

4.1.3.2. *Study Design*

A clear, concise description and evaluation of the study design is critical. Important aspects of study design include the number of subjects in each exposure group, descriptions of the study members, gender, route and duration of exposure, and outcomes assessed (including the timing of assessment in relation to exposure and life stage). It is helpful to highlight strengths and weaknesses in the study design, particularly in relation to life stage-specific assessments and how they influence issues identified in the problem formulation stage.

4.1.3.3. *Exposures*

An evaluation of the exposures to the study individuals (including exposure to humans or dosing/treatment to test animals) is particularly important for determining the adequacy of the study, interpreting the results and conclusions, and assessing the relevance and application of the findings to children's health risk assessment. It is important to characterize the manner in which exposures have occurred across the life stages of the study individuals. It is during this assessment that a determination can be made regarding whether the study has addressed the timing of exposure (e.g., exposure during preconception and critical windows of pre- or postnatal development). For example, in laboratory animal studies, if the toxicological evaluation characterizes adverse outcomes following exposures throughout childhood and to the time of adolescence, then study exposure methods may need to incorporate direct dosing techniques in juvenile animals (Zoetis & Walls, 2003). Additionally, the timing and the duration of exposure to test substance in 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 (Pinkerton & Joad, 2000; Holladay & Smialowicz, 2000; Peden, 2000; Dietert et al., 2000), the reproductive system (Pryor, 2000; Lemasters et al., 2000), the nervous system (Rice & Barone, 2000; Adams et al., 2000), the cardiovascular and endocrine systems (Osmond & Barker, 2000; Sadler, 2000; Hoet et al., 2000; Barr et al., 2000), and cancer/neoplasms (Anderson et al., 2000; Olshan et al., 2000). For epidemiological studies, consideration of, and iteration with, the exposure assessment phase (see Section 4.3) is necessary 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 needed.

4.1.3.4. *Outcomes*

A description of study findings, including the relationship of outcome to exposure, is a primary goal of hazard characterization. Especially important is the consideration of outcomes for specific life stages. The evaluation of each study needs to include whether and how study outcomes address issues raised during the problem formulation phase. For example, if the problem formulation specifically identifies a potential for exposure to pregnant women in a

residential setting, it is important to carefully consider any available human and animal data for outcomes following gestational exposures. The adequacy and limitations of exposure-outcome associations and their interpretation need to be considered carefully.

4.1.3.5. *Toxicokinetic (TK) Data*

Information on the TK profile may have been identified in the problem formulation phase. It is important to include and describe any available life stage-specific TK data, particularly, the relevance and impact of the TK data in evaluating the study, and in determining the impact of exposure and response across life stages. Toxicokinetic data can be used to verify that indirect exposure of the fetus or neonate (e.g., via maternal circulation or milk) occurred without relying on observable outcomes. In some situations, internal dose can be measured, providing greater accuracy in dose-response metrics. If toxicokinetic data are available across life stages, this information can aid in highlighting key life stages for assessment. For example, enhanced toxic response in the young can result from immaturity of specific metabolic enzymes or renal capabilities (e.g., elimination); information on the developmental profiles of enzymes or organ systems can help identify particularly susceptible ages.

Studies may find increased susceptibility of immature individuals but lack toxicokinetic data to assist in the interpretation of these findings. In that case, default assumptions are generally applied; 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 mom, or *3)* no age-related differences occur in absorption, distribution, metabolism and elimination (ADME), then the internal dose to the immature individual is equivalent to that of adults. However, these default assumptions may not be health protective; the availability and use of toxicokinetic data will likely decrease uncertainty in the risk assessment.

4.1.3.6. *Toxicodynamic (TD) Data*

TD data includes information about the steps between the toxicant's first interaction with the target organ and the toxic outcome. It is important to describe TD data for specific life stages, if available. Furthermore, examination of both TK and TD data may provide corroborative evidence of potentially susceptible life stages for a given chemical. For example, if TD information for a chemical suggests effects on the nervous system via decreasing

luteinizing hormone and disrupts the hypothalamic-pituitary-gonadal axis, greater concern would be warranted in the case when there are life stage-specific TK data demonstrating that the chemical is found in the brain, as opposed to the case when such data show that it does not cross the blood-brain barrier.

4.1.3.7. *Mode of Action (MOA) Information*

Consideration of MOA information (key TK and/or TD steps) is critical because it can be useful, for example, in: *1)* understanding the susceptibility differences among different life stages, *2)* determining the most appropriate animal model for relevance to humans or when outcome data for exposure during life stages are limited or not available for humans: *3)* predicting types of effects that might be seen during particular life stages, and *4)* predicting potential critical or susceptible life stages. For example, a given chemical that has as an anti-androgen MOA suggests that in utero and peripubertal intervals might be sensitive exposure windows for male reproductive outcomes. In this example, differences in androgen activity by life stage can explain the differences in susceptibility. It is also possible that the MOA for a given chemical differs among life stages. Although there are no known examples of this, it is one possible explanation when exposures during specific life stages and adult exposure lead to different outcomes. However, chemicals with more than one MOA, such as methoxychlor, have been described, and the different MOAs could be more or less active at different life stages.

4.1.3.8. *Detailed Qualitative Evaluation of the Dose-Response Data Profile*

A detailed qualitative evaluation of the dose-response profile is critical to interpreting the outcome for individual studies. For example, a clear dose-related toxicologic response helps support the judgment of whether an outcome is due to treatment. Determining the nature of adverse responses to an exposure can be an iterative process, because consideration of other studies in the database may highlight the importance of borderline or suggestive findings in individual studies and, ultimately, refine the interpretation of the data.

4.1.3.9. *Variability Analyses*

There are a number of sources of variability, both intrinsic and extrinsic, in toxicological and epidemiological data. Intrinsic variability (often termed “biological variability”) includes heterogeneity among individuals in a population or across life stages. It is expressed to some

degree in each parameter being measured. Examples of intrinsic variables for animal studies include strain, species, and other 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 variations in implementation. Examples of extrinsic variables for animal studies include handling techniques, ambient temperature, and noise, and for epidemiologic studies, variations in recruitment or data collection procedures.

Variability can be adequately and appropriately characterized by the statistical treatment of individual study data through, for example, calculations of central tendency. Nevertheless, although the degree of study variability may be controlled to some extent, high levels of variability may still be observed, which 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. High variability can sometimes render a study uninterpretable or result in reduced confidence in the veracity of the study findings, thereby decreasing the weight placed on the study for use in hazard characterization.

4.1.3.10. *Uncertainty Analyses*

Uncertainty from a variety of sources in life stage-specific data can affect the assessment of risk. Thorough consideration and description of the uncertainties for each study are essential. Any resulting assumptions, extrapolations, or speculative interpretations must be fully characterized. Uncertainties can result from data gaps (i.e., missing information) or inadequacies in the study protocol or methodologies, inadequacies in the reporting of study findings, or inconclusive results. Characterization of the uncertainties by life stage is important. Due to the iterative nature of the evaluation process and the consideration of information from multiple sources, data from other human or animal studies, data on structure-activity relationships (SARs), or TK or TD information, may be used to address uncertainties in a given study.

4.1.4. Evaluation of the Hazard Database

After relevant studies have been evaluated, those scientifically judged to be potentially useful for risk assessment (NRC, 1994) are selected and summarized, and the extent of the database is described. Best scientific judgment requires a well-justified decision to include a given study or exclude it from further consideration. Specific criteria can be developed for a particular assessment if appropriate. Characterization of the extent of the database includes a summary of the data gaps, uncertainties, and assumptions made in the assessment of the database as a whole (Figure 4-4). The adequacy, strength, and completeness of the database are considered. The adequacy of studies and characterization of the database are discussed in *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002b, Section 4.3). This information is then used to describe the WOE to identify potential hazards from exposures to children. A similar WOE approach in the assessment of environmental risks to children is described in the Office of Pesticide Programs report *Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment* (U.S. EPA, 2002c, Section III). The WOE analysis, described in more detail below, could be framed by factors presented in the conceptual model that was developed during the problem formulation phase (see Section 3.2).

4.1.4.1. *Summarizing the Hazard Database*

The overall hazard database includes detailed descriptions of all studies relevant to and critical for evaluating the hazard to children; all studies with developmental exposures, effects, or outcomes. It may also include in vitro data, MOA or mechanistic studies, and toxicity data in adults that help profile the toxicological response in children or provide support for assumptions made during the hazard characterization. A careful review of the studies' exposure durations and life stages may help in determining the relative importance (weight) of the studies in determining 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 life stages, and issues suggestive of differential susceptibility of children or specific life stages.

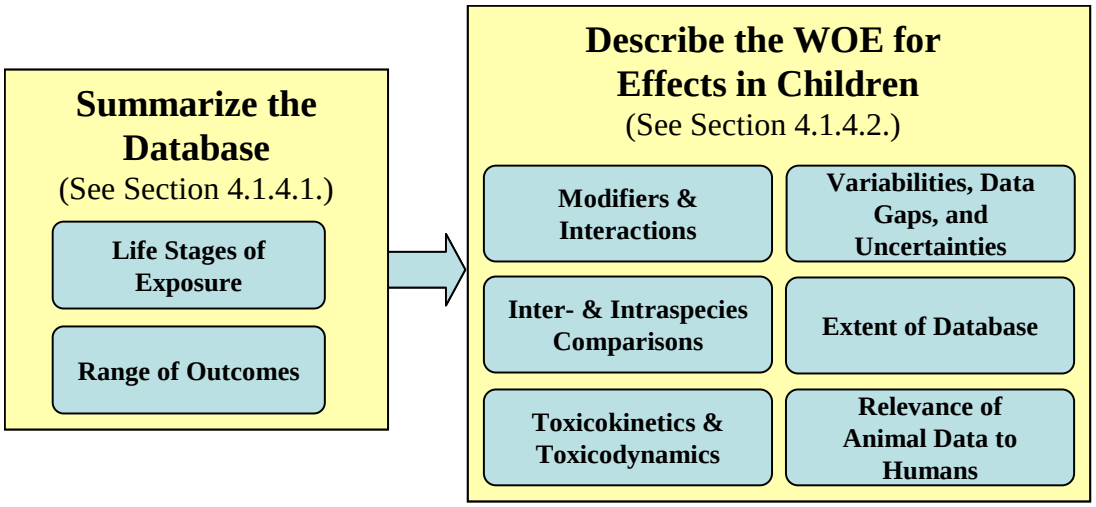


Figure 4-4. Hazard characterization Step 2: Evaluate the database as a whole for potential hazards to children from environmental exposures during different life stages. After each individual study has been evaluated, the second step in the hazard analysis is a consideration and integration of the entire database of studies. A narrative description of the database is generated, using a weight of evidence approach, with a focus on life stage-specific issues and considerations. This analysis becomes an integral component of the life stage-specific hazard characterization.

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. It is important to examine common links 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 life stages. The emphasis of the hazard summary is on the relationships (i.e., patterns) across observed outcomes, in relationship to life stages and mode of action.

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.

4.1.4.2. *Description of the Weight of Evidence (WOE)*

The WOE approach requires a critical evaluation (expert judgment) of all available data for consistency and biological plausibility. Criteria for this assessment are not presented here; rather, considerations important for the WOE are described. The key to WOE conclusions is the provision of a clear justification for decisions. Finally, the extent of the database is summarized, and assumptions made in the assessment are explicitly detailed. Further details about EPA's WOE 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, 2005b), and *Supplemental Guidance for Assessing Cancer Susceptibility from Early Life Exposure to Carcinogens* (U.S. EPA, 2005c). *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002b, Section 4.3.2.1.) and *Determination of the Appropriate FQPA Safety Factor(s) on Tolerance Assessment* (U.S. EPA, 2002c, Section III) provide additional detail on the WOE.

Key themes for the consideration of toxicity data in a WOE assessment, as adapted from Gray et al. (2001), are shown in Figure 4-5. This figure focuses on judging animal studies within a WOE assessment. However, if adequate human studies are available they would be given more weight. The process for evaluating these considerations is described in the following subsections. In this process, the quality of potentially relevant studies is judged, modifiers and interactions are detailed, outcomes across species are compared, TK and TD data are examined and weighed for comparisons across species, and the uncertainties and data gaps are determined. SARs with other chemicals or chemical classes are explored to determine the extent to which these data can inform the assessment via an MOA discussion or reduce uncertainties.

4.1.4.2.1. ***Modifiers and Interactions.*** Consideration needs to be given to effect modifiers and confounders in the studies. Then, questions of whether and how these have been evaluated in the data analysis are considered. It is important to focus on all potential life stage-specific effect modifiers and confounders and how they could affect the study outcomes or interpretation of study results. An example of an environmental modifier includes the influence of maternal health status (i.e., the effect of compromised maternal or offspring nutrition on development and maturation of the young).

4.1.4.2.2. ***Intra- and Interspecies Comparisons of Outcomes.*** For the chemical under assessment, any information on comparative species susceptibility for exposures and outcomes needs to be considered carefully, including comparisons between experimental animals and

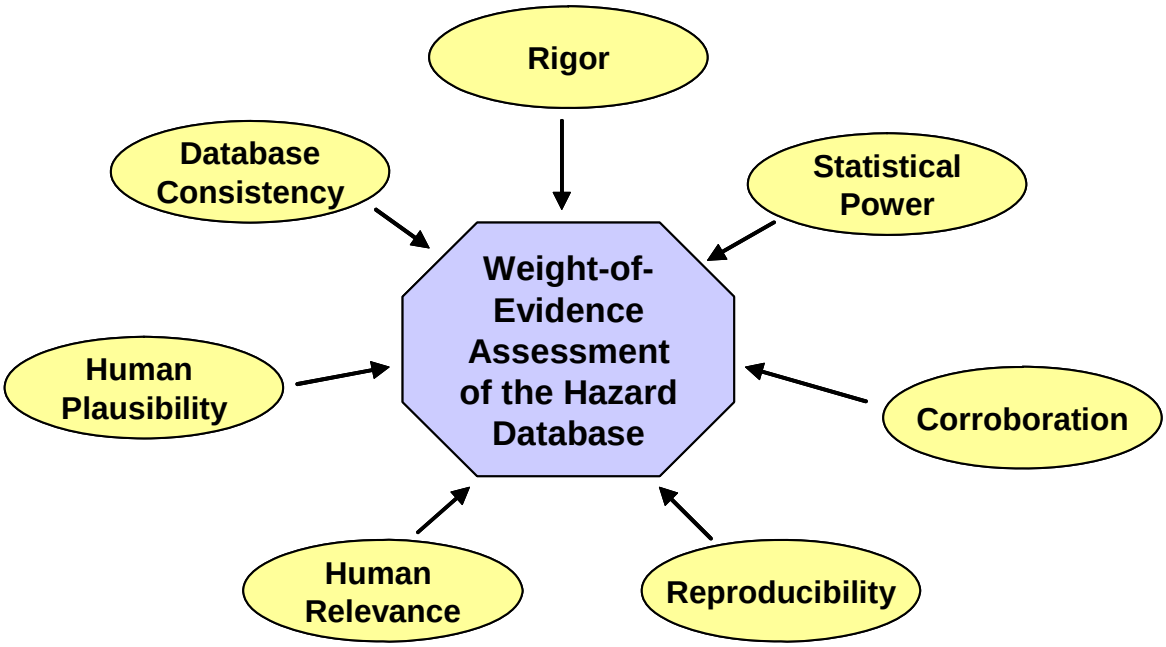


Figure 4-5. Conceptual view of a weight of evidence (WOE) assessment. This figure illustrates the critical considerations within a WOE assessment of toxicity data. *Rigor* is the degree of proper conduct and analysis of a study; greater weight is generally given to more rigorous studies. *Statistical Power* is the ability of a study to detect effects of a given magnitude. *Corroboration* means that specific effects are replicated in similar studies, similar effects are observed under varied conditions and /or similar effects are observed in multiple laboratories. *Reproducibility* means that an effect is observed in multiple species by various routes of exposure. *Relevance to Humans* means that similar effects are observed in humans or in a species taxonomically related to humans or at doses similar to those expected in humans. *Plausibility to Humans* is the determination of whether a similar metabolism, mechanisms of damage and repair, and molecular target of response could be expected to occur in humans, based on an evaluation of the biologic mechanism of a toxic response in animals. *Database Consistency* is the extent to which all of the data are similar in outcome and dose (exposure-response) and are operating under a single biologically plausible assumption (mode of action). (Source: Adapted from Gray et al. (2001)).

humans as well as comparisons across experimental animal test strains (Spearow et al., 1999, 2001) and species.

Important life stage-specific information to consider and use (if available) include:

- Comparative developmental stages between experimental animals and humans for the life stages when exposures or specific outcomes occur (i.e., what are the comparable developmental events among the species and strains),

- Cross-species and cross-strain similarities in outcome for comparable stages of development,

- Differences in developmental timing for certain species or strains that impact comparison of exposures during a given life stage for the database as a whole (i.e., certain rodent in utero exposure stages are comparable to certain human postnatal exposure stages), and

- The timing and route of exposures between animals and humans (e.g., whether the dosing interval in the test animal study is comparable to potential or actual exposure timing in humans).

A number of relevant papers comparing organ development across species are available for reference, as summarized in Hurtt and Sandler (2003a, 2003b). Beckman & Feuston (2003) compare landmarks in the development of the female reproductive system across species, and Marty et al. (2003) compare some key events in the postnatal development and maturation of the male reproductive system across species. Hew & Keller (2003) describe cross-species postnatal development of the cardiac system and life stage-related morphological and functional differences. Holsapple et al. (2003) address pre- and postnatal immune system development. Functional measures of postnatal central nervous system development are detailed in Wood et al. (2003). Zoetis and Hurtt compare anatomical and functional renal development (2003a) and lung development (2003b) across species. Postnatal bone growth and development is covered in Zoetis et al. (2003). Additionally, information on relative developmental timing across species for several systems is addressed in Selevan et al. (2000) and Hattis et al. (2004; 2005) for carcinogenesis.

4.1.4.2.3. ***Toxicokinetics (TK) and Toxicodynamics (TD).*** Available information on TK and TD similarities and differences between experimental animals and humans, across experimental animal models, or for various life stages are important to a children's health assessment and therefore, are described in detail. Consideration and decisions about how these data contribute to the evaluation and interpretation of the hazard database need to be addressed. In addition, data gaps need to be identified.

4.1.4.2.4. ***Variabilities, Data Gaps, and Uncertainties in the Database.*** The hazard characterization process requires a thorough assessment of the overall variabilities, data gaps,

and uncertainties that have been identified in the database, both generally and specifically for evaluation across life stages.

The sources of variability within individual studies are also confounding factors for the interpretation of data across or among studies. They can contribute to overall uncertainties in the database, including those that are applicable to the analysis of life stage-specific hazard. Variability of response across studies and possible reasons for the variability are important to assess and consider. For example, the response could vary among studies performed in the same animal species but using different strains. Further, 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.

A data gap is defined as missing information. In the evaluation of individual studies, data gaps may be identified that could have impact on the quality of the study, and these need to be considered in total when evaluating the data base. In addition, when combining the data from all the studies, data gaps for the comprehensive data base 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 peripubertal period. If this were the case, then a data gap in coverage of this particular developmental life stage of exposure is highlighted. For any chemical assessment, there will be inevitable gaps in the available life stage-specific information. The relative impact of missing or inadequate information to the overall goals of the assessment needs to be judged. In some cases, information gleaned from the toxicological profiles of structurally related chemicals or chemicals with a similar MOA may assist in interpreting the relative importance of a data insufficiency, or in some cases it can even provide a way of bridging a data gap (Julien et al., 2004). When evaluating life stage-specific uncertainties and data gaps, it is important to address study design, including measurements, exposure, and outcomes across life stages (U.S. EPA, 1991, Section 3.1.2.1;1996, Section 3.3.1.5; 2002b, Section 4.3.1). The results of individual study assessments and the consideration of those studies during the summarization of the database and the WOE assessment will help to focus this analysis. Examples of questions that could help to focus the evaluation of life stage-specific data gaps and uncertainties are provided in Appendix 1.

Finally, the description of data gaps and uncertainties can be framed from the perspective of the problem formulation. For example, if the problem formulation analysis suggested that

infants had high risks due to biological susceptibility or their probability of exposure, then the absence of data to characterize the hazard and dose-response information for that life stage would affect the relevancy of the risk assessment to address the identified problem or question of the assessment (as defined in the Problem Formulation phase). Additionally, information from the exposure assessment could be critical when identifying any remaining uncertainties in the hazard characterization.

The characterization of data gaps also includes a determination of whether required studies are present (those that are required by statute or convention, e.g., a rodent and a non-rodent prenatal developmental toxicity study and a reproduction and fertility effects study). In addition, uncertainties arising from the absence of any other data identified as critical to an adequate assessment of hazard and dose-response for the specific chemical risk assessment need to be addressed. The potential qualitative and quantitative impact of these missing data on the risk assessment (e.g., on the POD) is considered in both the hazard characterization and dose response assessment phases, because this information may be important in determining the need for or the magnitude of a database uncertainty factor (UF) during dose-response assessment (U.S. EPA, 2002b). Sometimes, other types or sources of data can assist in satisfying an identified data gap. As one example, if for a chemical being evaluated, there are no data relevant to the assessment of hazard following exposure during a particular life stage (e.g., the perinatal period), data from a similar life stage 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.

4.1.4.2.5. ***Extent of the Database.*** The report *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002b) recommends summarizing the extent of the database and gives broad definitions for the range from a "minimal" to a "robust" database (p. 4-19). These definitions were intended to define the range, of database characteristics, with minimal including the least amount of information that would be sufficient to conduct a risk assessment and robust as the "gold standard" that fully characterizes the potential toxicity of a chemical or group of chemicals. The intent is for the assessors to characterize and justify in a narrative form the extent of the database, including data gaps and uncertainties (e.g., life stage-

specific exposures and outcomes, TK and TD data, the types of outcomes evaluated, reversibility, and latency to response) that aid in determining the extent of the database.

For an assessment across life stages, the extent of the database as a whole is then evaluated from the perspective of the conceptual model (developed in the problem formulation phase). In considering the extent of the database, the quality, quantity (i.e., studies available to evaluate), and uncertainties and data gaps in the assessment are considered.

4.1.4.2.6. ***Relevance of Animal Data to Humans.*** Adequate human data are, of course, the most relevant for assessing risks to humans. Nevertheless, a major default assumption that is used in the absence of human data is that experimental animal data are relevant for humans. This concept is integral to the EPA risk assessment guidelines for developmental toxicity, reproductive toxicity, neurotoxicity, and carcinogenesis (U.S. EPA, 1991, 1996a, 1998b, 2005b, 2005c). A key step in the assessment is the characterization of assumptions and uncertainties of the animal database and the use of these data for predicting risk in humans. Based on the WOE, there is strong support regarding the likelihood of effects in humans when *(1)* the dose-response relationship demonstrates a predictable change in effect as a function of dose (or exposure), *(2)* qualitative and quantitative comparability exists in the TK or metabolism between animals and humans, *(3)* effects are similar across more than one animal species or between animals and humans, *(4)* a homologous MOA in experimental animals and humans has been demonstrated, and *(5)* the temporal relationship between exposure and effect is consistent (U.S. EPA 2002b, pp. 4-13 to 4-14).

Discussion of the following issues can be important: the relevance to humans, specifically to children, and the dose-response relationship at doses that are relevant to exposure at developmental life stages (i.e., environmental levels). A WOE description of these points will be used in the life stage-specific hazard characterization phase (see Section 4.1.5).

4.1.5. Life Stage-Specific Hazard Characterization Narrative

In this final step in the hazard characterization (Figure 4-6), a scientific rationale for the selection of outcomes relevant for use in quantitative dose-response assessment are clearly and concisely summarized. Included in this assessment are considerations of life stage-specific

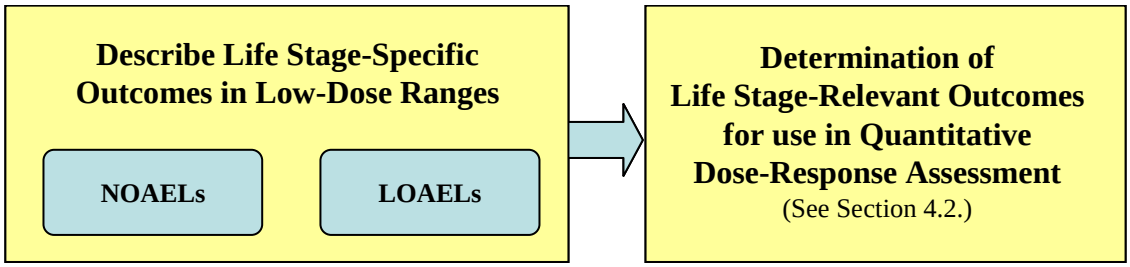


Figure 4-6. Hazard characterization, Step 3: Describe and determine life stage-relevant outcomes. In the third and final step in the hazard characterization, life stage-relevant outcomes in the lower dose ranges are described for use in the next analysis phase, the quantitative dose-response assessment. Different low dose ranges (e.g., no observed adverse effect levels (NOAELs) and lowest observed adverse effect levels (LOAELs)) may have been identified for different outcomes or for different life stages of exposure depending upon different routes and durations of exposure.

outcomes, including susceptibility of individuals; the impact of interindividual variability on response; and remaining uncertainties in the hazard evaluation. Issues to consider include:

- Life stage-specific outcomes from the whole database that were identified in the lower dose range(s) (not just a single "critical effect"). (If there are data, no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs), benchmark doses (BMDs) and BMD lower confidence limits (BMDLs), or data supporting other quantitative approaches like quantitative risk estimates (QRE) then this information is subsequently considered in dose response analysis.)
- Life stage-specific outcomes relevant for use in quantitative dose-response assessment.
- The most susceptible life stages (e.g., women of childbearing age [preconception and fetuses], breastfeeding infants, or toddlers and older children) from the available data. Justification for the most susceptible life stage(s) can be provided by data to support the relevant outcomes of concern.
- The development of margin of exposures (MOEs) through iterations among the hazard characterization, dose-response, and exposure assessment phases.

This information will subsequently be used in the dose-response assessment phase (Section 4.2.). Finally, in risk characterization (see Section 5), the life stage-specific hazard characterization information and exposure assessment information are important components for describing risk to children.

4.2. DOSE-RESPONSE ASSESSMENT

4.2.1. Introduction

4.2.1.1. *Scoping of the Dose-Response Assessment*

Figure 4-7 presents a framework for developing a dose-response characterization for developmental life stages. The process begins by summarizing the available data and culminates with a descriptive characterization of the data, models, estimates, and uncertainties applied. In selecting the appropriate dose-response model for life stages, careful consideration of routes of exposure, toxicokinetics (TK), toxicodynamics (TD), epidemiological findings, and mode of action (MOA) is critical. Where available, resources for aiding a life stage dose-response analysis are provided so that risk assessors are aware of some of the guidelines, scientific literature, and other useful resources for this phase of analysis in children's health risk assessment.

4.2.1.2. *Extent of Assessment*

Risk assessment is a broad term with different meanings in different contexts. In the past, different approaches have been used to characterize risk, depending on whether the outcomes were cancer or noncancer effects. More recently, a harmonized approach is advocated in an attempt to characterize outcomes as either having a threshold (i.e. nonlinear) or non-threshold (i.e., linear) mode of action. This harmonized approach recognizes that both cancer and noncancer endpoints can appropriately be characterized as threshold or non-threshold depending on the available data. Risk assessment processes also vary somewhat on exposure scenario, i.e. duration, route, and source. Regardless of these differences, a life stage approach can be utilized in risk assessments. During the problem formulation, the scope and breadth of an assessment are established and generally fall into two categories, narrow and broad. In an assessment with a relatively narrow scope, outcomes for specific life stages thought to be at risk are analyzed. In a broad scope assessment, each life stage is analyzed in the pursuit of a more thorough "cradle to grave" assessment. Such a broad scope assessment, however, is not intended to characterize risk at each individual life stage, but rather characterize risk for the most sensitive

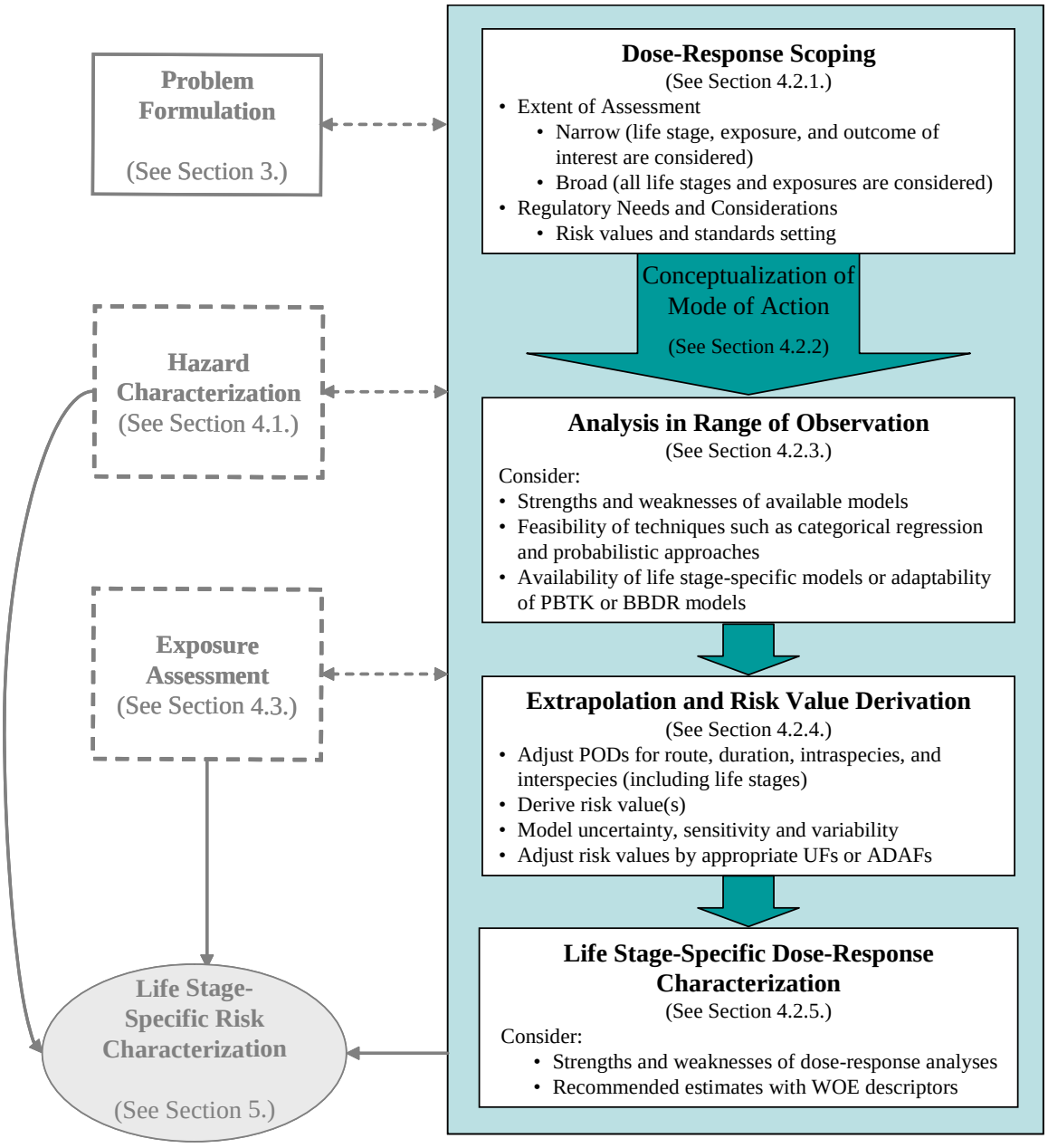


Figure 4-7. Flow diagram for life stage-specific dose-response assessment. This figure illustrates the flow of information and analysis that comprises dose-response assessment. As illustrated by the solid arrows, hazard characterization, dose-response assessment, and exposure assessment contribute to the risk characterization. The problem formulation phase establishes the context of the risk assessment and feeds into the scoping process to identify the extent of the assessment and the output needed. Selection of the dose-response relationships for life stages of interest is made, and appropriate extrapolations and risk value derivations are performed and subsequently described in the dose-response characterization and risk characterization. Throughout dose-response assessment, repeated iterations (dashed arrows) with the problem formulation, hazard characterization, and exposure assessment phases identify the need to collect more data or conduct more detailed analyses. *Abbreviations:* PBTK, physiologically based toxicokinetic; BBDR, biologically based dose-response; PODs, points of departure; UF, uncertainty factors; ADAF, age dependent adjustment factors; WOE, weight of evidence.

life stage for the appropriate exposure scenario. Regardless of the breadth of the assessment, the exposure scenario, or hypothesized mode of action of the environmental agent, the life stage approach can add to the overall soundness and confidence in the assessment, as well as provide a thorough as possible starting point for future reassessments.

4.2.1.3. *Regulatory Needs and Considerations*

Based on the needs outlined in the problem formulation of a given risk assessment, an approach for carrying out a chemical risk assessment is developed. The approaches will include methodologies and standard setting protocols. It is important to re-emphasize that the nature and number of risk estimates is governed by the problem formulation and hazard characterization. Under a narrow scope assessment (see Section 4.2.1.2), risk may need only be characterized for one life stage, exposure scenario (e.g., acute, oral exposure) and outcome (e.g. leukemia). Alternatively, under a broader scope assessment, risk may need to be characterized for the most susceptible life stages for each exposure scenario of interest. In either approach, age-specific information on factors related to exposure and response are needed.

Risk values are typically categorized on route and duration. Acute toxicity is of particular concern in children because the complex processes of embryogenesis, fetal and postnatal development provide ample opportunities for toxicant exposures to alter the regulation of development. Perhaps less apparent, however, is the applicability of long-term risk values to children. For instance, reference dose (RfD) and reference concentration (RfC) values are risk estimates calculated for various routes (oral, dermal, inhalation) and durations (acute, short-term, chronic) of exposure (U.S. EPA, 2002b). It is important to note that chronic exposure is defined as exposure up to 10% of lifetime; thus, chronic risk values (RfVs) may be applicable to children, because seven years of exposure meets the EPA definition of chronic human exposure (U.S. EPA, 2002b). Unit risk estimates such as cancer slope factor (CSF) are used to define the exposure concentration that yields a given level of risk (e.g., 1×10^{-6}) during a lifetime. Although the latency of time to tumor may mask detection of cancer from exposures occurring in early life stages, early exposures may indeed increase the risk of tumor development in later life stages. In fact, there is evidence to support the notion that susceptibility to tumor development from exposure to mutagenic chemicals during earlier life stages is greater relative to later life stages (U.S. EPA, 2005c). Depending on the goals stated in the problem formulation of a risk

assessment, the literature database should be assessed for studies that have examined cancer in adult humans and experimental animals following early life exposure.

4.2.2. Mode of Action (MOA) Conceptualization

Dose-response analysis can proceed along two paths, one which is informed by MOA information or one where quantitative risk values are developed with little or no insight into the MOA of an environmental toxicant. A more informed assessment, however, utilizes the 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. In fact, these data are an important part of the hazard characterization and help to establish the MOAs underlying the various dose-response relationships. MOA is increasingly recognized in the scientific community as a foundation from which to build a dose-response analysis (Andersen & Dennison, 2001; Andersen et al., 2000; Clewell et al., 2002a; Preston, 2004). In order to conceptualize a MOA, it is necessary to summarize the dose-response model(s) available, the mechanistic data that relates the critical effect(s) of interest to a particular dose metric, and the data supporting the choice of a likely or hypothesized dose metric.

4.2.2.1. *Summarizing the Available Dose-Response Relationships*

Route and duration make up the exposure element for individual life stages. Although the problem formulation will have likely identified exposure scenarios that pose risks to individual life stages, a quantitative risk assessment requires identification of dose-response relationships from which to begin quantifying risk for scenarios and life stages of interest. This process presents a critical interface with the exposure assessment, where source-to-dose modeling informs assessors about the relevant range of likely external exposure for different exposure scenarios and specific life stages. Because low-dose extrapolation has inherent uncertainties regarding MOA over dose ranges (Slikker et al., 2004a, 2004b), the exposure assessment can help inform selection of the appropriate dose-response model from which to obtain a point of departure (POD). It is also important to realize that analysis of dose-response data could (under certain circumstances) warrant re-examination of the exposure assessment. 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 critical than initially thought and perhaps be an impetus for further characterization and refinement of exposure models employed for predicting external doses.

An exposure-response array can help identify critical outcomes (U.S. EPA, 2002b, 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 a MOA. Alternatively, different effects across dose ranges may represent a gradient of effects operating through common mechanisms, and thus also lend support to a MOA. 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. Using this array, multiple responses can be described as a continuum of dose, and may be informative in risk management. An alternative approach is to assign key outcomes to severity categories and analyze by categorical regression (see Section 4.2.3.1).

The complexities of developmental processes require that equal consideration be given to the life stage at which critical effects (i.e., outcomes or responses) are observed. In circumstances where data exist for multiple life stages, it is likely that effects at earlier life stages pose greater risk, a priori, due to the potential for irreversible changes or changes that confer an increase in risk to subsequent exposures in later life stages[3]. It is for this reason that dose-response selection should be informed by MOA considerations in addition to the available response data. This provides an important interface with the hazard characterization. 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. Similarly, effects identified or proposed may have implications for choosing dose-response models that are most relevant to the life stages of interest.

There is also opportunity for dose-response analysis to inform hazard characterization. For instance, toxicologists adept at hazard characterization may not have the requisite skills to thoroughly evaluate certain models such as PBTK models. Therefore, it is possible that situations could arise where a thorough analysis of a PBTK model by modeling experts indicates that the model inadequately predicts empirical data. This could be due to either deficiencies in the model, or could suggest that the dose metric previously hypothesized to be associated with a

[3] 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 event in later childhood (Greaves, 2003).

response may not be the appropriate dose metric responsible for the toxicological outcome; the latter instance could potentially prompt a reconsideration of the dose metric or MOA. In addition, this could be an impetus for instead using the empirical data against which the model was evaluated, and for proceeding with the assessment in the absence of a clearly defined MOA.

Exposure and response considerations for examining plausible MOAs include the following:

- Have exposure scenarios and various life stages (e.g., preconception, pregnancy, infancy, childhood been addressed? Are there data concerning early life exposures related to latent adult effects data?
- Are any known developmental windows likely to be affected by exposure? What is known about pre- and post-pubertal exposures?
- Have individual physiological and developmental processes been compared with the child behavioral development; i.e., how do life stage behaviors and exposure scenarios compare with individual physiological parameters such as enzyme ontogeny and renal clearance maturation? (*It is possible that maturation of such parameters spans multiple behavioral stages. In such cases, behavioral susceptibilities and physiological susceptibilities might require time weighting to assess exposure to the dose metric.)*
- Are the various outcomes likely linked by MOA or are they different? Do the outcomes share common mechanisms? Do the outcomes represent a gradient of the same MOA?

4.2.2.2. *Mechanistic Data and Mode of Action*

The complexity of development provides opportunity for toxic exposures to create TD effects that may or may not be relevant to adults. Developmental stages or age groupings may 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 life stages and across species. Examples of organ system development include the respiratory, cardiovascular, central and peripheral nervous systems, and immune systems.

Comparison across species and life stages might allow for identification of systems that might be at risk during comparable windows of exposure, and inform the decision of which effects and dose-response data are most useful. Across species, matching comparable life stages is necessary in order to limit TD differences in the critical response of interest (see Section

4.2.4.2). Within species, studies suggest that there is concordance of cancer outcomes across life stages, albeit with different potencies (U.S. EPA, 2005c; Hattis et al., 2004). Although the results of such studies may lend some confidence in extrapolating effects from adults to children, data also indicate the potential for differential tumor responses depending on life stage of exposure (U.S. EPA, 2005c). It is not clear, however, whether these differences relate solely to differences in metabolic activation. Considerations include:

- Are TD effects known or hypothesized? Are the key players (e.g., receptors, DNA repair enzymes) involved in the known or suspected MOA expressed sufficiently during the life stage of interest? (*As stated above, concordance for cancer outcomes is fairly well documented; although this implies a similar MOA, it is important to address, if possible, whether the same molecular events are responsible.)*

- Based on developmental susceptibilities, have the available studies addressed all possible outcomes of concern (e.g., cognitive deficits, immunological effects, endocrine disruption.)? Are there data that support the notion that such outcomes are likely to be relevant for the life stage of interest?

4.2.2.3. *Selection of Dose Metric*

Selection of the appropriate dose metric is an iterative process. In instances where only a few metabolites are formed from a parent compound, the chemical nature of these metabolites might aid in the formulation of a plausible MOA. In other instances, particularly when there are numerous metabolites, data from biochemical and toxicological studies may be the primary driver for formulating a plausible MOA. In practical terms this may not be the toxic moiety at the target tissue, but often will be a surrogate such as blood concentration of a particular moiety (parent or metabolite). The underlying assumption in dose-response analysis is that the dose metric will exact the same effect at equivalent doses irrespective of species and route, provided there are no TD differences (Andersen & Dennison, 2001; Clewell et al., 2002).

Clewell et al. (2002) have proposed two criteria for dose metric determination. The first criterion is that the dose metric must exhibit plausibility, which they define as consistency with MOA and ability to simplify a complex dose-response relationship. The second criterion is conservatism, defined as the selection of the dose metric that poses the highest risk or the lowest acceptable exposure level (Clewell et al., 2002). It is important to recognize that a potent dose metric is not synonymous with a potent exposure/applied dose, and it is the environmental

exposure level to humans that is regulated. For this reason, the choice of dose metric should be that which results from the most potent exposure/applied dose. After a dose metric is selected, interspecies and intraspecies extrapolations can be applied by adjusting physiological and TK parameters (see Section 4.2.4.2.). This might include enzyme activity levels (K_M and V_{max}), relative comparisons of expression levels of xenobiotic metabolizing enzymes, levels of cofactors, and physiological parameters (e.g., liver blood flow). Age-related differences in absorption, distribution, metabolism, and elimination have been reviewed (Besunder et al., 1988a, 1998b; Clewell et al., 2002b; Clewell et al., 2004) (see Section 4.2.3.1.). Considerations include:

- What is the human exposure scenario (route, duration, and pattern)?
- How will chemical-specific factors interplay with the route? *(Reactive gases are thought to primarily have effects at the portal of entry; thus, life stage differences in respiratory rate and tract surface area can be made. Non-reactive gases act more systemically; thus, blood: air partition coefficients, cardiac output, and tissue partition are important considerations. Additionally, plasma protein binding, gastric pH, intestinal pinocytosis, mucocilliary function, skin thickness, and irritation, and other parameters will govern several TK factors, and these are likely to differ across life stages.*
- Will the distribution differ across life stages and species? (*Lipid and water content, protein binding, membrane transporters, immaturity of the blood brain barrier, and as other parameters will likely alter the volume of distribution and half-life for many compounds.)*
- What are the metabolic differences among (and within) species and life stage? What does the ontogeny of the xenobiotic metabolizing enzymes involved in the dose metric formation and termination predict for the dose metric level and time course? (*Generally speaking, enzyme levels approach those of adults within the first 6 months of life. Evidence suggests, however, that drug clearance in children may be higher than in adults thereafter. It is important to consider how enzyme ontogeny will affect activation or detoxification, as well as how tissue localization and blood flow will affect these factors. Additionally, cofactor levels may impact TK; glutathione levels*, e.g., *may differ across life stages.)*
- What is the likely role of maternal and fetal TK factors?

4.2.3. Analysis in the Range of Observation

Data for dose-response analysis in the range of observation come in many forms, from empirical PODs derived from either a no observable adverse effect level (NOAEL) or a lowest observable adverse effect level (LOAEL) to sophisticated models incorporating mechanistic data. The nature and amount of data required for each type of dose-response analysis might be said to represent a hierarchy, although the more sophisticated dose response models still rely on the same 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. Briefly summarized below are some of the dose-response models available to risk assessors. These models are typically employed in order to determine PODs, which are used for extrapolations in dose-response analysis and MOE analysis in risk characterization. In *Guidelines for Carcinogen Risk Assessment* (U.S. EPA 2005b), the U.S. EPA has adopted an approach that advocates the use of as much biologically-informed dose-response data as possible, and suggests that older "default" approaches be used only in instances where little data exists concerning an environmental toxicant of interest. Physiologically based toxicokinetic (PBTK) and biologically based dose-response (BBDR) models are techniques that 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 Data and Models in Risk Assessment* (U.S. EPA 2005a). Furthermore, their use in conjunction with statistical modeling is perhaps the most rigorous[4]. The following brief descriptions summarize the types of analyses used in risk assessment, generally from those based on limited data sets to those requiring very rich data sets for dose-response analysis.

4.2.3.1. *Dose-Response Models*

Traditional approaches to dose-response modeling of a toxicant with a 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 toxicological studies. Two main disadvantages of using these single point estimate values is that they do not consider the shape of the dose-response curve, nor do they allow for

[4] Such an approach was used in a risk assessment for ethylene glycol monobutyl ether (U.S. EPA 1999b), where experimental dose conditions were converted to internal dose, followed by benchmark dose analysis.

estimation of risks at any exposure level of interest (Allen et al., 1998). Thus, the use of NOAEL and LOAEL values alone represent the bottom tier of dose-response models and are used most often when limited data is available concerning the toxicant of interest.

A more sophisticated approach for determining PODs is the use of benchmark dose analysis (Crump, 1984)[5]. This approach attempts to fit statistical models to existing dose-response data regardless of whether the MOA is linear or nonlinear, but often requires studies with more dose groups and a higher number of subjects. For this reason, BMD is usually performed when the scientific database for an environmental chemical is relatively large. An advantage of the BMD methodology is that statistical models can take into account all of the data points in a dose-response study; thus, unlike the NOAEL/LOAEL approach, the BMD is influenced by the shape of the dose-response curve (Allen et al. 1998). The BMD is defined as the dose at which a predetermined change in response incidence (e.g., 5% or 10% change in critical effect) occurs; with the 95% lower confidence bound being the BMDL. Because the BMDL is a function of 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 (Barnes et al., 1995; Allen et al., 1998). For further readings on choosing studies for BMD analysis, refer to *Benchmark Dose Technical Guidance Document, External Review Draft* (U.S. EPA, 2000a).

One limitation to BMD analysis is that the analysis can only be performed on individual studies (Brown & Strickland, 2003). Categorical regression[6] analysis, on the other hand, is similar to BMD analysis but can be performed on combined studies. In this method, data is pooled from different studies (possibly with different endpoints) that are "assigned" to the same severity category (Brown & Strickland, 2003). An advantage to this approach is that a small number of studies (possibly even studies of different duration) can essentially be combined into one larger study, and thus can narrow the confidence limits (Brown & Strickland, 2003)[7]. Although studies of different duration may be problematic (particularly when dealing with short windows of susceptibility), this methodology may be particularly important in a life stage

[5] EPA has developed software for BMD analysis; available from: http://cfpub.epa.gov/ncea/cfm/bmds.cfm

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

[7] It should be noted that severity categorization may require expert judgment, and thus may be subject to differing opinions.

approach where it is likely that fewer studies will have been performed on the specific life stages of interest or critical windows of susceptibility.

Physiologically based toxicokinetic (PBTK) and biologically based dose-response (BBDR) modeling are perhaps the most amenable modeling technique for using a life stage approach, as they are designed to mimic true biological processes and model whole organisms. Knowledge and understanding of absorption, distribution, excretion, and elimination (ADME) are essential for estimating delivered dose. Behavioral, anatomical, and metabolic differences during each life stage require modification of available adult models. Several reviews have described the variation in TK factors between adults and children (Besunder et al., 1988a, 1988b; Bruckner, 2000; Clewell et al., 2002a; Hines & McCarver, 2002; McCarver & Hines, 2002). Although the use of TK models for internal dose estimates is increasing, more effort is needed in developing such models for children's dosimetric adjustments across life stages and species. Some models available in pediatric pharmacology could be appropriately applied for some portions of certain risk assessments. For instance, general knowledge of differences between adults and children in metabolic clearance of CYP3A-specific pharmaceutical substrates could be utilized by incorporating this difference into an adult TK model when the toxicant is thought to be metabolized by CYP3A (Ginsberg et al., 2004a, 2004b). Ginsberg et al. (2002) compiled a database of 45 drugs for which TK data are available across life stages; this database can be accessed at http://www2.clarku.edu/faculty/dhattis.

PBTK models can be used to conduct route-to-route extrapolations, duration adjustments, interspecies extrapolations, as well as life stage extrapolations. Particularly useful, is the fact that these models can mimic any exposure scenario (continuous or otherwise). 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

Although PBTK models may be particularly useful in periodic exposure modeling, they are not necessarily applicable for extrapolating from short-term exposure studies to longer-term predictions because the key events leading to the observed responses are not likely to be impervious to the effects of time. Many dose-response relationships may be dependent on temporal changes in TD processes due to developmental- and exposure-induced changes;

examples include cell proliferation rates, DNA repair processes, receptor tolerance and desensitization, and age-related changes in physiological parameters. Importantly, many early developmental windows are relatively short; thus extrapolation from short-term exposure scenarios to longer-term scenarios requires consideration of whether the same windows of susceptibility are likely to be operable.

Application and review of PBTK models in risk assessment can be found in (Ginsberg et al., 2004b; Pelekis et al., 2001; U.S. EPA 2005a). There are some early life stage 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 & Gearhart 2002; Clewell et al., 2003). Several pregnancy and lactation models have been reviewed (Corley et al. 2003).

BBDR models represent the state of the art in dose-response analysis, 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 & Dennison 2001; Ashani & Pistinner 2004; Setzer et al., 2001). In addition to life stage-specific TK data, the relationship between the internal dose metric and response may require life stage-specific TD data. Currently, relatively few BBDR models are available due to the inherent complexity of integrating TK and TD data, as well as more practical limitations to BBDR model development, such as model transparency, quality criteria, and limited shelf-life of some models beyond initial publication (DeWoskin et al., 2001). It is expected that their use will increase as toxicological studies go beyond more frank effects and move toward molecular precursor events (Andersen & 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[8]. 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,

[8] It should be recognized that compounds with common toxicodynamic effects need not be structurally related.

two chemicals might be hypothesized to affect similar TD processes, 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 (see Figure 4-8).

Probabilistic risk assessment has typically been used in exposure assessment. This approach, however, is increasingly being applied for dose-response assessment as data become available for physiological parameters such as genetic polymorphisms in TK and TD pathways (Beck et al., 2001; Pelekis et al., 2003). 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 timeframe, or at a specific location. Similarly, life stage-specific parameters can be employed in order to estimate the variability in dose and response among subpopulations such as infants and children.

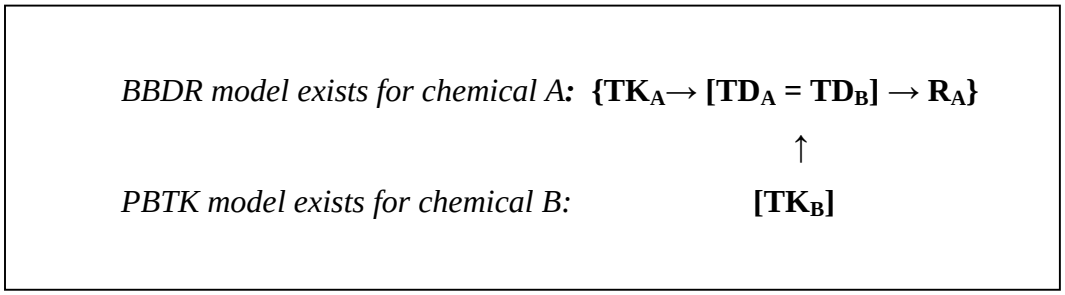


Figure 4-8. Generalized biologically based dose-response (BBDR) model. The top line in this figure represents a BBDR model for the dose-response of chemical A, where TK_A, TD_A, and R_A represent the toxicokinetic, toxicodynamic, and response of interest related to chemical A, respectively. In this scenario, the toxicodynamic of chemical B (TD_B) are thought to be equivalent to those of chemical A (i.e. both have the same mode of action from a toxicodynamic perspective). If a physiologically based toxicokinetic (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.

One limitation applicable to many of the aforementioned dose-response modeling approaches, in regards to noncancer endpoints, is that the analyses are based on toxicological endpoints as opposed to public health outcomes. Quantitative risk estimation (QRE) is a broad-based method for relating human exposures to non-toxicological endpoints. 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 is that 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 between 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, 2005e). An inherent disadvantage to this approach is that acceptable levels of risk must be defined, whereas other approaches to non-cancer dose-response modeling arguably rely less on value judgment.

4.2.4. Extrapolations and Risk Derivation from a Life Stage Approach

After PODs have been established from various dose-response studies or modeling techniques, low dose extrapolation is performed in order to derive measures of risk. Again, this may be done for assessments of narrow or broad scope, and will have important regulatory implications (Figure 4-7). To this end, various adjustments are made in order to extrapolate to the exposure scenarios and life stages 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 have been informed by and are supported by empirical evidence. For example, empirical analysis supports the use of body weight scaling (see below) to adjust for pharmacokinetic differences across species. Additionally, the use of more sophisticated techniques does not necessarily result in refinements of final 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, 2003f). Despite the fact that this may be a possible outcome, the use of sophisticated techniques, MOA information, and life stage analyses certainly improve the confidence that risk values are health protective.

4.2.4.1. *Duration and Route Adjustments*

Animal exposure studies, almost always being discontinuous, require 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 that can determine (*in silico*) an applied dose (continuous or otherwise) that results in the same AUC or C_{max} as that was likely to have been generated in the test animal under the original laboratory study conditions. This may require parameterization with life stage- and species-specific data. As stated in section 4.2.3.1, 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.

For route-to-route extrapolation, default equivalent dose adjustments can be used. Standard mg/kg/day adjustments assume similar TK and TD processes; 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 incorporation of route-specific TK factors. An important limitation, however, is that route extrapolations are not useful in instances where the critical effects are portal of entry specific. For more on route and duration adjustments, see *Approaches for the Application of Physiologically Based Pharmacokinetic Data and Models in Risk Assessment* (U.S. EPA, 2005a) and *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002b).

4.2.4.2. *Interspecies and Intraspecies Adjustments*

The EPA RfC process describes the interspecies adjustment from animals to human equivalent concentration (HEC) via dosimetric adjustment factors (DAFs), (U.S. EPA 2002b). For oral exposures, default interspecies extrapolation based on body weight scaling, either body weight (BW^1) or body weight to the ¾ power ($BW^{¾}$), have been employed. In particular, $BW^{¾}$ 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, 2002b). Recent harmonization efforts at EPA advocate the adoption of $BW^{¾}$ scaling for RfD derivation in instances where there is limited data with which to perform an assessment. This has been proposed in an effort to harmonize oral RfD methodology with RfC methodology with the use of DAFs, as well as with oral cancer assessments with the use of $BW^{¾}$ scaling.

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 be determined experimentally and theoretically (U.S. EPA, 2002b). In the absence of DAFs, simple ventilation rate adjustments can be made for HECs. Finally, it is important to note 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 2002b). Consider:

- Should the same interspecies factors be applied in deriving HECs and human equivalent doses for all life stages? *The answer here is equivocal, because more empirical data are needed. A priori, rates of deposition, mass transfer, flow limited diffusion, and partition coefficients are likely to be affected by life stage-specific differences in anatomy, skin composition, lipid/water ratios, and volumes, and protein binding can affect diffusion of compounds (e.g., plasma protein binding affect on the glomerular filtration rate, GFR). Although age-specific data are needed, the problem is exacerbated by the fact that these values are a function of both species- and chemical-specific properties, and thus may require both chemical- and life stage-specific data.*

In addition to interspecies adjustments, $BW^{3/4}$ scaling may also be useful for intraspecies adult-child adjustments. Data from pharmaceutics indicate that TK processes (e.g. chemical half life) in children may also scale to $BW^{3/4}$, particularly in children over 2 months of age (Ginsberg et al., 2002, 2004a, 2004b; 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, life stage considerations can be included in two general ways, each with its own advantages and disadvantages. Essentially, these involve either intraspecies adjustments or interspecies extrapolation. Adjustments across human life stages from adult to earlier developmental stages requires 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, PBTK models developed for adult humans (if available) could be parameterized in order to predict the

dose metric in children. 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 young 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 humans species; on the other hand, this approach requires that the underlying toxic response and MOA are concordant across life stages. This assumption, if not well-supported by data, may add a large degree of uncertainty to the dose-response analysis.

More often, however, the data needed for life stage extrapolation will be available only in animals and thus will often require both qualitative and quantitative adjustments (Barton, 2005). Qualitative adjustments include determining the developmental stages in test 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 & Sandler, 2003a, 2003b; Selevan et al., 2000). 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) life stages. For instance, rodents are born at an overall developmental stage roughly equivalent to end of the second human trimester. Thus if equivalent windows of susceptibility exist at these two different life stages 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 developmental studies) as opposed to assuming concordance of effects across life stages. This will likely have the effect of reducing the interspecies UF due to TK adjustments, as well as due to a general increase in confidence that TD differences (if they exist) have been minimized. One caveat, however, is that human data (from controlled exposures or epidemiological studies) with which to test the predictive capability of the model will often be 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.

Because the majority of data concerning a chemical will pertain to nonhuman species, TK and TD data are crucial elements for life stage-specific dose-response characterization. It is for this reason that PBTK and BBDR models have been emphasized for dose-response modeling under the life stages approach. There are several examples where existing adult models have been adapted to early life stages. 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., 2002), some of which are modeled to account for growth throughout gestation. Physiological parameter values were derived from numerous previous publications[9]; this model was used to derive RfD and RfC values based on developmental outcomes. Pelekis et al. (2003) demonstrated the use of a life stage 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, however, take into account age-related differences in exposure, nor are TD factors addressed. Life stage data have also been used in BBDR modeling. For instance, a BBDR model has been developed for relating 5-fluorouracil exposure at gestational day 14 to birth defects in rats. This models 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).

4.2.4.3. *Low-dose Extrapolation*

Caution should be used when using the shape of the dose-response curve for deciding upon the appropriate means of low-dose extrapolation. Although human data, particularly from children (if available), may be extremely important for establishing a POD for risk derivation in a life stage context, it should be realized that epidemiological data often exhibit linear dose-response relationships. Lutz et al. (2005) have provided evidence that this linearity may, in part, be a result of interindividual genetic and life style differences, as well as other issues related to

[9] Currently, several efforts are underway to develop life stage physiological parameters databases that will provide a comprehensive and authoritative resource for use in risk assessment.

epidemiological studies such as difficulties in dose reconstruction. Conversely, Lutz et al. (2005) also demonstrated that animal bioassay studies that suggest a threshold effect may also 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 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, 2005b) advocate a MOA approach to low-dose extrapolation of cancer endpoints, 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 for cancer endpoints is used when the MOA can be demonstrated to result from a threshold (i.e. nonlinear) MOA. Nonlinear extrapolation approaches are also used for noncancer endpoints, although methods for risk based approaches to noncancer endpoints, and their relevance to cost-benefit analysis, have been proposed (Gaylor & Kodell, 2002; Clewell & Crump, 2005).[10] In addition, there may also be biological support for low-dose linear extrapolation for noncancer endpoints. For example, 1,2-dibromo-3-chloropropane is thought to reduce sperm count by interaction with DNA; thus, as is employed for mutagenic carcinogens, there is scientific rationale for using low-dose linear extrapolation for compounds that cause noncancer effects through interaction with DNA, and potentially other MOAs as well.

4.2.4.4. *Model Uncertainty, Sensitivity, and Variability*

Models are approximations of biological processes and therefore have inherent shortfalls. Model uncertainty comprises that which is unknown about how well a model reflects the underlying biology[11]. Uncertainty analysis can have both quantitative and qualitative

[10] Some program offices do set standards using risk based approaches for noncancer endpoints.
[11] See the draft *Approaches for the Application of Physiologically Based Pharmacokinetic Models and Supporting Data in Risk Assessment* (U.S. EPA, 2005a) for an in-depth treatment of PBTK model evaluation.

components. 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 animal test species or the applicability of animal species to the human life stage of interest (see discussion in section 4.2.4.2). These particular efforts enhance the scientific underpinnings of the dose-response analysis and are explicitly carried forward in the dose-response narrative (Section 4.2.5) through to the risk characterization (Section 5.1.2).

Sensitivity analysis allows risk assessors to examine which parameters in a model are most critical to the final outcome. This analysis is a key evaluation technique for PBTK models. This analysis can identify the key parameters that should be further examined for accuracy, either through available data or estimation. In addition, selection of sensitive parameters could help in identifying more susceptible life stages. For instance, model sensitivity to ventilation rate provides an important starting point for addressing life stage differences.

Variability analyses evaluate the range of values for a parameter in a population. This is particularly useful when sensitivity analysis has identified a key parameter as having an important 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, 2005a). This type of analysis, for instance, allows assessors to predict upper and lower bounds on a dose metric level in a test species; thus multiple calculations of the relevant exposure concentration for humans could be calculated and perhaps used for subsequent risk derivation.

It is particularly important that model evaluation not be a final step in the risk assessment process. Sensitive parameters provide red flags that should be examined carefully for variability of these parameters within the population. Alternatively, the sensitivity might suggest the need for careful examination and consideration of susceptible life stages.

4.2.4.5. *Risk Value Derivation and Application of Uncertainty Factors (Including Age-Dependent Adjustment Factors)*

A detailed outline for derivation of risk values is beyond the scope of this framework. Risk assessors should consult EPA guidelines for procedures and policies for deriving risk values

and applying UFs. Current practices for RfC and RfD derivation and the application of UFs are outlined in *A Review of the Reference Dose and Reference Concentration Process* (U.S. EPA, 2002b). As stated in Section 4.2.4.2, life stage extrapolations for risk derivation, depending on the initial data from which the extrapolation is based, will affect the magnitude of the UFs applied in the final risk value derivation. New guidance on CSF derivation from early life exposure to environmental agents can be found in the *Supplemental Guidance for Assessing Cancer Susceptibility from Early Life Exposure to Carcinogens* (U.S. EPA, 2005c). In brief, the new guidance states that for toxicants acting through a mutagenic MOA, where data concerning early life susceptibility is 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 to 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, to analyses indicating an increased incidence of tumor formation from early life exposure as compared to adult exposure. For an explanation of the choice of these values and age groupings see *Supplemental Guidance for Assessing Cancer Susceptibility from Early Life Exposure to Carcinogens* (U.S. EPA, 2005c).

Historically, life stage-related uncertainties have been folded into the database UF when the MOA is nonlinear. It must be reiterated that life stage-specific data gaps do not necessarily imply a greater database UF; rather, the method should help focus attention on the most critical data gaps deserving of additional uncertainty weighting. Indeed, the rationale for using the life stage approach is to better characterize individual risk and thus decrease uncertainty in risk assessment.

4.2.5. Life Stage-Specific Dose-Response Characterization Narrative

Following derivation of final risk values, a dose-response characterization summarizes the dose response information to be used in conjunction with the exposure information for a full characterization of risk. This characterization is a narrative description that provides a summary of recommended estimates, data supporting those estimates, modeling approaches, a POD narrative, key default assumptions, and identification of susceptible life stages or sensitive

subpopulations and quantification of their susceptibility. A discussion of the strengths and limitations of the dose-response assessment should be presented, highlighting significant issues in developing risk values, including alternative approaches considered equally plausible, and how these issues were resolved. It is important that all estimates be accompanied by the descriptors used in the WOE narrative. For instance, a toxicant may be described as "likely to be carcinogenic to humans" when exposed by "oral route" (U.S. EPA, 2005b). In this regard, risk managers will be able to put each estimate into context.

4.3. EXPOSURE ASSESSMENT

4.3.1. Introduction

The following section presents a comprehensive approach for characterizing children's exposures to environmental contaminants. The outline for assessing children's exposure follows the steps presented in Figure 4-9. The process begins with scoping of the exposure assessment within the context of the broader risk assessment problem formulation. This step refines the planning and scoping described in section 3.1 by adding the exposure components. The exposure components include identifying the sources of the chemicals or agents of concern, the relevant exposure pathways (including media and route) by which children may be exposed, and the exposure scenarios specific to children. The preliminary evaluation of sources, pathways, and scenarios allows the assessor to refine the goals, the breadth, and the focus of the overall risk assessment. For example, the assessment questions may change on the basis of the exposure pathways identified during the scoping phase of the exposure assessment. Depending on the risk assessment objectives, it may be important to involve stakeholders at this point in the assessment to ensure that their concerns are addressed. The conceptual model is then enhanced by adding more details describing how relevant exposures may take place. The conceptual model is used to identify available exposure information including chemical properties, environmental fate and transport mechanisms, media concentrations, and population characteristics and behaviors. The available exposure information is used to conduct a life stage-specific exposure analysis. Generally, a tiered approach is used beginning with a screening-level assessment and then, refining the assessment if necessary to provide more detail for potentially important scenarios or potentially vulnerable age groups. The last step in the exposure assessment process is the life

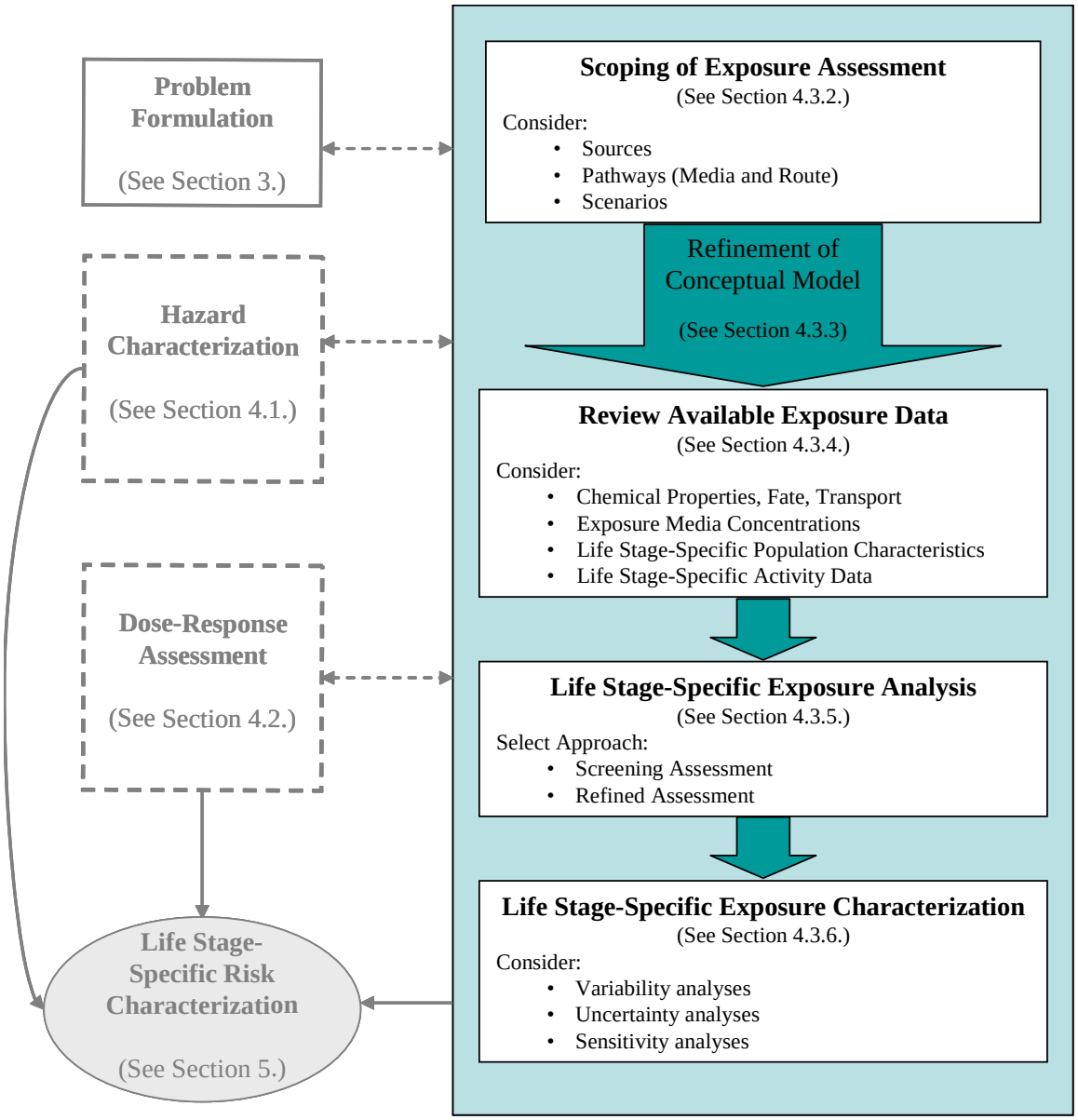


Figure 4-9. Flow diagram for life stage-specific exposure assessment. This figure illustrates the flow of information and analysis that make up exposure assessment. The process begins with a scoping phase to identify the sources, pathways, media, and scenarios that are more relevant to children's exposures to the particular environmental contaminant, taking into consideration the questions identified in the problem formulation. The scope assists the assessor in the development of a conceptual model that describes how the exposure takes place, with consideration of life stages. The conceptual model is followed by the review of the available exposure data for the life stages of interest. Iteration with hazard and dose-response assessments (illustrated by dashed arrows) can occur throughout this process to ensure that critical windows of exposure are considered. Exposure is then estimated using a tiered approach. This tiered approach begins with a screening-level assessment followed by a more refined level of analysis if necessary. Finally, the life stage-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. As illustrated by the solid arrows, hazard characterization, dose-response assessment, and exposure assessment contribute to the risk characterization.

stage-specific exposure characterization where the results, analyses, and conclusions are summarized.

Each of these steps is coordinated with the hazard and dose-response characterization. For each step in the exposure assessment process discussed below, a series of guiding questions is presented to ensure that all relevant environmental exposures are included in the qualitative and quantitative evaluation of risk to children. The exposure information described below is used to develop estimates of dose. The estimates of dose are later integrated with the dose-response assessment to develop estimates of likelihood of adverse effects in children who are potentially at risk. The primary conclusions about the exposure assessment include a discussion about the variability and uncertainty in the dose estimates. This discussion feeds into the risk characterization, where the results from hazard, dose, and exposure are integrated and confidence about the conclusions is discussed.

4.3.2. Scoping of Exposure Assessment

4.3.2.1. *Sources*

Much of the information essential for characterizing sources will be similar for any risk assessment. The exposure assessor should place particular emphasis on identifying sources in the places where children spend time, which may change by developmental stage. For example, sources may be identified in: *(1)* residence and workplace for pregnant and lactating women; *(2)* residence, daycare and outdoor play areas for infants and toddlers; *(3)* residence, school, and locations of after-school activities for school-age children; and *(4)* residence, school, and locations of after-school activities and workplace for adolescents.

- Are there any chemical or agents that are of special concern for children?
- What are the chemicals or agents of concern?

4.3.2.2. *Pathways*

For a given source, exposure media and exposure routes can define the pathways. Exposure media include air, water, soil/dust/sediments, food, and objects/surfaces; exposure routes include inhalation, ingestion, dermal absorption, and indirect ingestion (non-dietary and indirect dietary routes) (U.S. EPA, 2002a, 2003a.). The result of this evaluation 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 change with life stage. For example, the fetus will be exposed to cord blood and amniotic fluid, the infant to breast milk, the teething child to many objects (both intended and unintended) for mouthing, the school-age child to pesticides used in the classroom, and the adolescent to vocational or recreational hazards.

- What are all the potential exposure media?
- What are all the potential exposure routes?
- What are the potential exposure pathways in the conceptual model? What are the specific pathways that may be of concern for children?
- How are the chemicals or agents getting from a source to the receptor child?

4.3.2.3. *Scenarios*

For any given pathway, a set of associated exposure scenarios describes how an exposure takes place. This information is used to estimate distribution of exposure by any given pathway. An exposure scenario is defined by the combination of the following details (adapted from Hubal et al., 2000):

- What are the relevant sources of exposure?
- What are the potentially exposed populations (e.g., age or developmental stage)?
- What is the relevant time frame of exposure (e.g., acute, short term, chronic, intermittent)?
- What are the potential locations of exposure (e.g., residence, school, outdoors, indoors)?
- What are the potential activities (e.g., mouthing, playing soccer, mowing lawns) that may lead to exposure?

Potential exposure scenarios should be identified at this point on the conceptual basis of the exposure model as well as the problem formulation for the life stage risk assessment. Once available data are evaluated, additional scenarios may be added.

4.3.3. Refinement of the Conceptual Model

The exposure assessment component of the conceptual model for children's risks described in Section 3.1 would need to consider important life stages. Within each life stage there may be a series of developmental periods for which exposure would need to 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), other potential windows of susceptibility identified through the hazard characterization (e.g., those during prenatal development), or windows of potentially high exposure due to age-specific behaviors and physiology (e.g., crawling, teething). Several important life stages would need to be considered in exposure assessments for children (Figure 4-10):

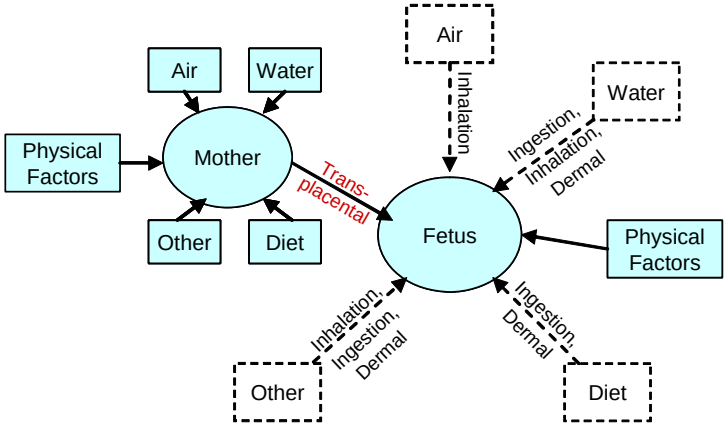
- Are there possible parental preconception exposures?
- Might there be exposure during the pregnancy that affects embryonic/fetal stages?
- Are there possible exposures during infancy and early childhood?
- Are there possible exposures during older childhood and adolescence?

Typically, the conceptual model will consider human exposure in the context of the source-to-effects paradigm (U.S. EPA, 2003c, 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 subpopulations 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-effects 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 population being exposed. As a result, only populations with exposure to this specific source are included in the model. Yet, exposure may result from multiple independent sources, all of which could be used to generate information on total exposure to a chemical or mixture of chemicals. In this case, a person-oriented exposure assessment better characterizes the person or population of interest and the applicable sources (Figure 3-2).

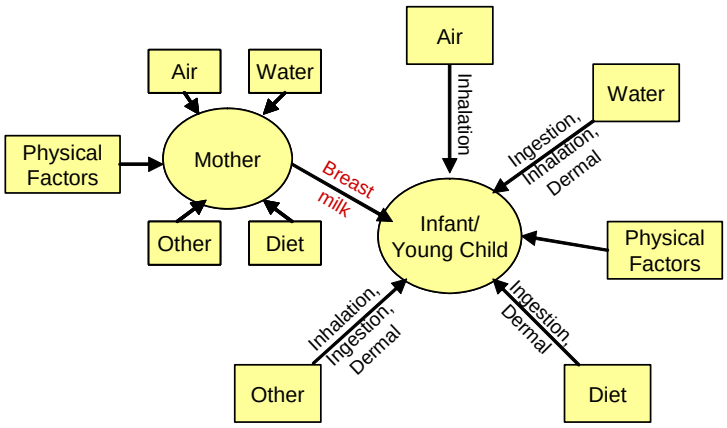
Prenatal:

All exposures to the fetus occur transplacentally or via physical factors. The mother's exposure to environmental media can be a significant source of exposure for environmental media for the fetus.



Infant/Young Child:

Exposures for the infant and young adult can occur through all environmental media. When breastfed, the mother's exposure to environmental media can be an additional source of exposure to the infant.



Older Child/Adolescent:

Exposures to the child and adolescent can occur through all environmental media. The mother's exposure is no longer a factor for the child.

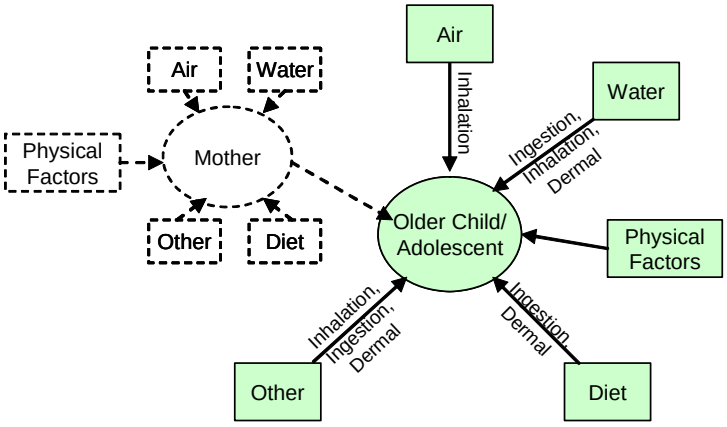


Figure 4-10. Exposure routes during developmental life stages. These three figures show the different routes of exposure by life stage for children. The solid lines in the figure represent relevant exposure, while dotted lines represent exposures that are not relevant to the specific life-stage. During 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.

Since this approach puts children in the center as the population of interest, it is particularly useful in focusing the assessment to address the following issues:

- What child-specific questions is the assessment trying to answer?
- How are parents and/or children being exposed, from the source to the absorbed dose for all pathways of exposure?

4.3.4. Review of the Available Exposure Data

Exposure data are used to estimate distributions of exposure in the exposed population. In children especially, different factors might affect the child's dose. Some questions to get at these issues include:

- What types of exposure data are available for infants and children (direct or indirect measurements of exposure)?
- Are children's activity data available?
- Are there biomonitoring data that demonstrate exposure potential and that can be used to estimate an individual's exposure level?
- 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)?

4.3.4.1. *Chemical Properties, Fate, and Transport*

Once a chemical is released into the environment, it can change chemically or be transported from one place to another. Scientists and engineers can predict the environmental movement of a chemical by its chemical properties, (e.g., volatilization rate, water solubility, soil/water partitioning coefficients). In addition, it is important to know the conditions of the environment that may affect the chemical's fate and transport. These conditions include for

example: soil characteristics, amount of rainfall, wind direction, and presence of water bodies. Some questions to consider include:

- What are the release rates? What is known about the manufacturing processes that may lead to information on releases?
- 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, etc.) that may affect the fate and transport of the chemical(s)?
- 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?

4.3.4.2. *Media Concentrations*

Media concentrations refers to the amount of chemical present in an environmental (e.g., soil, water, air, food) or biological medium (e.g., blood, hair, urine, breath). It is critical to give special considerations for the 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. Important questions to consider include:

- Are environmental measurements available (e.g., contaminant concentrations in the exposure media in which the child spends time)?
- If monitoring data are not available, are there models that can be used to predict the concentration at the exposure point?
- Are biomonitoring data available? *(These data are useful for quantifying exposures if the relationship between the substance found in the body and the amount of substance the child was in contact with can be established.)*
- What are the concentrations of the chemicals that will be contacted by the child during an exposure period?
- How are the concentrations changing over time?

4.3.4.3. *Life Stage-Specific Population Characteristics*

For children, behavior varies by developmental stage, and this may have a significant impact on exposure. Children should be classified and exposure assessed for each age grouping (age bin) to characterize all relevant scenarios for children's risk (i.e., to identify highly exposed populations). Currently, EPA's ***Draft Guidance on Selecting the Appropriate Age Groups for Assessing Childhood Exposures to Environmental Contaminants* (U.S. EPA, 2003b)** should be used as a starting point for identifying and selecting age bins for analysis (see Table 4-1). This guidance provides a detailed discussion of how these age groups were developed and how they should be implemented 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 in children.

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. 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, p. 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* (EPA, 1996 Section 3.3.1.5.3, pp. 60–61).

The following questions could be considered in order to characterize life stage-specific populations:

- What groups are exposed (e.g., general population, highly exposed groups, highly susceptible groups, specific life stages)?
- What are the adverse health effects of importance to the population of interest? How do these inform the identification of exposures of greatest importance for the observed outcomes?

Table 4-1. Developmental life stages and age groups for exposure assessments

Life Stages	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
	6 to <11 years
Adolescent	11 to <16 years
	16 to <18 years
	18 to <21 years [b]

[a] The age groupings from birth to adulthood are from U.S. EPA, 2003b.
[b]These age groupings were arrived at by the behavior subgroup of the Technical Workshop (U.S. EPA, 2000b) considering key factors or "major domains of behavioral development" for each route of exposure these are to be considered on a case by case basis.

- Are there any highly exposed age groups?
- 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)?
- What are the child-specific exposure factors necessary to characterize the exposure scenarios?
- What are the ranges or distributions of exposure factors?

Although the focus of this section is the examination of vulnerability associated with differential exposure due to life stage, it is recognized that it is impossible to completely separate

consideration of vulnerability due to life stage from consideration of vulnerability due to other key individual and community characteristics. 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 and exposure assessment.

4.3.4.4. *Life Stage-Specific Activity Data*

It is important to characterize activities and behaviors that result in significant exposures (e.g., breastfeeding, mouthing, sports, after-school employment) for each life stage (associated with age bins and with other important characteristics of the group). The most current version of *Child-Specific Exposure Factor Handbook* (U.S. EPA, 2002a) could be the starting point for identifying these values. Age-specific activity data are also available from the *Consolidated Human Activity Database (*CHAD) available online at http://www.epa.gov/chadnet1/. Some considerations to include:

- What activities of the parent or child may result in exposure?
- What developmental stage-specific behaviors may lead to contact with the chemicals? How do the behaviors vary among children of various ages?

4.3.4.5. *Iteration of the Review of Data with Hazard and Dose-Response Characterization*

As discussed in EPA's *Framework for Cumulative Risk Assessment* (U.S. EPA, 2003a), vulnerability to environmentally mediated health effects can[0] vary on the basis of susceptibility, differential exposure, differential preparedness, and differential ability to recover[0]. The key issue is how to capture these changes in an assessment of risks from exposure to environmental contaminants. In conducting the hazard and dose-response characterization portion of a risk assessment, the assessor must consider critical windows within development that result in greater vulnerability to toxic effects. In developing the exposure assessment, the assessor must also consider windows of vulnerability based on, for example, behaviors (crawling, mouthing), activities (locations, product use, diet), and physiological characteristics (oxygen requirements, caloric requirements) that may lead to particularly high levels of exposure. For example, information on the environmental fate of a compound and a child's subsequent contact with it is

critical to ensure that hazard information is relevant to the measured exposure. As another example, understanding the dosimetry of an absorbed agent can inform the temporal resolution needed in the exposure data and assessment. The hazard, dose-response and exposure analyses are combined to identify the life stages that are at greatest risk.

The focus of the exposure assessment is to identify age groups and address vulnerability resulting from differential exposure. Because the focus here is on exposure or potential dose, TK considerations (i.e., ADME) are not explicitly considered unless they have direct impacts on potential dose (e.g., absorption at the portal of entry). However, it is impossible to completely separate consideration of exposure and potential dose from consideration of internal dosimetry and response. This is the reason why hazard assessment, dose-response assessment, and exposure assessments are intimately linked.

Initial hazard information could be used to guide problem formulation (scoping) for the exposure assessment. After a preliminary exposure assessment, the hazard characterization may need modification. The following questions identify those issues that might suggest changes in the initial hazard characterization:

- 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?
- What other crosscutting issues may need to be considered at this stage in the assessment?

4.3.5. Life Stage-Specific Exposure Analysis

Exposure estimates may be developed for all relevant life stage-specific scenarios. The data identified in Section 4.3.4 are used to estimate exposure for all of the potentially important pathways and scenarios identified in the conceptual model (Section 4.3.3). At this point in the assessment, vulnerable age groups will be identified, patterns of exposure will be characterized (e.g., intermittent, continuous, acute, or chronic), and exposures levels will be quantified. Identifying children with potentially higher exposures or significant exposures during critical windows is critical for a complete exposure assessment for children. These considerations are of particular interest when assessing children's exposures because the timing of exposure can affect the outcomes observed. Children may experience unique exposure patterns that would need to be considered in relation to their critical windows of development.

The health effect of concern would need to be considered when selecting the appropriate temporal scale for estimating exposure/dose. 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, 2003b). Assessments of agents with multiple sources or in multiple media may require additional work to estimate children's exposure patterns. This means that, even at the screening level, 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 may be needed for all but the most basic assessments.

To conduct the life stage-specific exposure analysis, a calculation approach described in section 4.3.5.1 is selected on the basis of available data and the risk assessment questions that were defined during the problem formulation stage. Often, two or more calculation approaches will be used and the results compared in the exposure characterization stage. Typically, an exposure analysis will begin with a screening-level assessment 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. This type of tiered level analysis discussed in Section 4.3.5.2 is often used to facilitate efficient allocation of resources.

4.3.5.1. *Exposure Measurement and Estimation Approach*

Three approaches may be used to calculate exposures: the point-of-contact approach, the scenario evaluation approach, and the dose reconstruction approach.

Point-of-contact approach: Sometimes referred to as the direct approach, this 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. It does not take into account an individual's characteristics.

Scenario evaluation approach: Sometimes referred to as the indirect approach and it requires data on chemical concentration and frequency and duration of exposure, as well as information on the exposed population. Child-specific behaviors and physiologic characteristics may be assumed on the basis of exposure factor data (U.S. EPA, 2002a) or from exposure study databases (the Consolidated Human Activity Database [CHAD], available from http://www.epa.gov/chadnet1; the Human Exposure Database System [HEDS], available from http://www.epa.gov/heds), 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.

Dose reconstruction approach: This 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 allow simplification of risk assessment; however, only a few examples currently exist for applying this approach successfully. At the present time, biomarker data are difficult to interpret, either because the presence of a biomarker may not be unique (many stressors may 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

4.3.5.2. *Analysis Level or Tier*

Typically, an exposure analysis 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. The first tier described below is a screening-level assessment used to identify and prioritize potentially important exposures. The screening level assessment uses bounding values for exposure factors and conservative simplifying assumptions. Therefore, the output may have a high level of uncertainty. After results of the screening assessment are compared with results of the hazard characterization, a more refined assessment may be required to reduce uncertainty in the initial exposure estimates. The 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. The major difference between the two levels of assessment described below is related to the assumptions that are used. The screening level uses bounding assumptions, and resulting exposure estimates may have a high degree of uncertainty. In the refined assessment, more realistic estimates of exposure are developed for selected scenarios to reduce the uncertainty. It is important to note that probabilistic techniques may be used at either level of analysis depending on the types of scenarios that are being evaluated. Finally, if a high level of uncertainty remains around estimates of exposure following a refined assessment, supplemental data collection may be needed.

4.3.5.2.1. ***Screeening Assessment.*** The purpose of a screening tier is to identify important pathways and scenarios, as well as 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, 2001a).

In the screening-level analysis, important differences in exposure between children of different developmental stages are identified. For some specific exposure scenarios and compounds, combining some of the age groups may be appropriate, for example, where variation in exposure factors and resulting exposures is insignificant (U.S. EPA, 2003b).

Limited data may be a critical impediment in conducting assessments for each of these age groups and for making decisions regarding combining or eliminating age groups. In these cases, the recommended age groups (U.S. EPA, 2003b) should be used unless qualitative

information leads the assessor to identify potentially significant differences within a recommended age bin. 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 following questions could be considered.

- Do these results address the questions posed in the problem definition stage of the risk assessment?
- What are the bounding assumptions used to identify potentially important sources, pathways, and scenarios?
- What is the potential magnitude of exposures?
- How do potentially important scenarios and potentially vulnerable age groups compare with critical windows identified in the hazard characterization?
- How do potential exposure levels compare with hazard levels (e.g., margin of exposure)?
- 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 versus factor of 2 or 3)?
- Is the information currently available adequate? What criteria are used to determine adequacy? What are the significant data needs? Is there a need to collect additional data?

Based on the bounding assumptions used in this level of analysis and comparison with the hazard analysis, a set of potentially significant exposure scenarios for important age groups will be identified. In order to identify and understand the important 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 are 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 the next section.

4.3.5.2.2. ***Refined Assessment.*** This tier provides more detail for potentially important scenarios and potentially vulnerable age groups. The goal is often to estimate the distribution of exposure for each of the important life stages. 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.

- Again, do these results address the questions posed in the problem formulation stage of the risk assessment?
- 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 assessment results?
- Which groups of children present the highest exposures on the basis of their current developmental stage?
- Is the exposure information currently available adequate? What criteria are used to determine adequacy? What are the significant exposure data needs? Is there a need to collect additional data?

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 (see 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 the Food Quality Protection Act (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.

It is important to note that few of these models are designed currently to specifically address life stage 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 life stage assessment. This issue is discussed further in *Draft Guidance on Selecting the Appropriate Age Groups for Assessing Childhood Exposures to Environmental Contaminants* (U.S. EPA, 2003b).

Limitations of the data, model results, and associated uncertainties are considered and addressed in the refined analysis. For example, were the exposure data adequate to sufficiently investigate and identify important differences across the age groups? Available exposure data sets may not allow modelers or risk assessors to directly extract data from the underlying sources to conduct age group-specific analyses. Potential approaches to address this issue include *1)* reorganizing the exposure input data set to conform to the age groupings needed, *2)* 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 *3)* 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.

The assessor may reconsider:

- What are the available 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?

4.3.5.2.3. ***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 assessment be addressed, collection of new data to address them may be needed.

4.3.6. Life Stage-Specific Exposure Characterization Narrative

The results of the exposure assessment should be summarized in a narrative that includes a discussion of the results, analysis, and conclusions derived from the analysis. More importantly, the narrative should include a discussion of the key assumptions, limitations, and uncertainties associated with the exposure estimates and any potential bias in the results. Results of the uncertainty analysis and sensitivity analyses should also be discussed. The variability in the population can be presented by providing ranges or distributions of the exposure. It is useful to also include a description of how the assessment can be improved and uncertainties be reduced by additional research or collection of data.

It is important that the results of the assessment are communicated in a clear and concise manner to the risk manager, and include considerations of childhood variability and uncertainty within the exposure analysis. The following questions could also be considered by the assessor.

- If different approaches were used to estimate exposure for different life stages or within a life stage, what were the results? Can they be compared and, if so, how do they compare? Which approach is more appropriate?
- Does the life stage-specific assessment capture the variability in the exposed groups? What are the ranges or distributions of exposure?
- What are the uncertainties in the estimates, both within and across life stages?
- What are the data limitations and how do they compare across life stages?
- What data gaps exist, both within and across life stages? 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 life stages? Could the exposure estimates be refined if more data were available?

4.3.6.1. *Variability Analyses*

Distinguishing between uncertainty and inter individual variability is an important issue in exposure assessments for children. Variability refers to the lack of uniformity in a population. It is an inherent characteristic of the population that cannot be reduced with additional data. Differences among individuals in a population are referred to as inter individual variability. Differences associated with an individual overtime are referred to as intra individual variability.

Among children, inter individual variability can be important due to rapid physiological and behavioral changes. Even within a relatively narrow age group, variability may be large. This variability affects the determination of upper percentiles of exposure and its associated risk, and so can be critical to children's risk assessment. 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.

Variability in children's exposure and dose is due to differences in behavior and physiology. 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 activity level and breathing behavior (e.g., the transition from mouth to nasal breathing), for example (U.S. EPA, 2003b). 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. Physiological characteristics affecting variability in exposure/dose include anatomical characteristics (e.g., body weight and proportion of body fat) and specific organ and physiological systems (e.g., skin, skeleton, liver, immune system, reproductive system, renal system, cardiac system, central nervous system, muscle, and sensory organs). For example, infants have immature immune systems, and renal functions are less than those predicted by surface area (U.S. EPA, 2003b).

4.3.6.2. *Uncertainty Analyses*

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 or with 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. Data for children under 2 years of age are lacking. Uncertainties need to be 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. General issues to consider when applying these quantitative methods are described in EPA's *Guiding Principles*

for Monte Carlo Analysis (U.S. EPA, 1997b). An EPA workshop was held in 1998 to discuss issues regarding the selection of input distributions for probabilistic assessments (U.S. EPA, 1999a). 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).

4.3.6.3. *Sensitivity Analyses*

Sensitivity analysis has been defined as the assessment of the impact of changes in input values on model outputs. Its main purpose in any exposure assessment 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 important 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 life stage-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.

4.4. SUMMARY OF ANALYSIS PHASE

This section presented a comprehensive approach for characterizing children's exposures to environmental contaminants. This life stage-specific analyses results in a thorough characterization of the magnitude, frequency, and duration of exposure received for various exposure pathways. The results of the exposure assessment are then combined with the results from the hazard and dose response analysis to characterize potential risks to children. The conclusions from the exposure assessment and the discussion about key assumptions, limitations, and uncertainties are later integrated with the conclusions from the hazard and dose response assessments to provide a characterization of risk.

5. LIFE STAGE-SPECIFIC RISK CHARACTERIZATION

Risk characterization is the final phase of the risk assessment process, in which the hazard, dose-response, and exposure assessment components of the risk assessment are integrated, summarized, and major conclusions are drawn. Risk characterization should be done in accordance with EPA's science policy handbook on risk characterization (U.S. EPA, 2000c), which provides detailed guidance for EPA staff. Other sources of information that were consulted in the development of this risk characterization section were the developmental toxicity, reproductive toxicity, neurotoxicity and cancer risk assessment guidelines (U.S. EPA 1991, 1996, 1998b, 2005b, 2005c) and the National Research Council's report *Science and Judgment in Risk Assessment (NRC, 1994)*.

As with other sections of this framework, the issues to be addressed in risk characterization are pointed out in a list of questions that guide the assessor through this process, with particular focus on the life stage-specific issues. The following lists of questions are a modification of those developed the for risk characterization of reproductive toxicity risk assessment guidelines (U.S. EPA, 1996). The information for these questions is assessed and described in the analysis phases and used in the risk characterization narrative.

5.1. SUMMARY OF THE MAJOR CONCLUSIONS IN LIFE STAGE-SPECIFIC RISK CHARACTERIZATION

This summary includes a narrative of the major conclusions from the analysis phases of this framework with a concise description of the major qualitative and quantitative aspects, including discussion of critical windows of development identified in the hazard assessment and the associated exposure assessment. This nontechnical narrative describes the overall picture of health risks resulting from children's exposures, based on the hazard, quantitative dose-response, and exposure characterizations. The assumptions and uncertainties should be clearly identified and described. In addition, significant data gaps that could affect the respective major conclusions should be identified and described. Finally, the summary provides the qualitative and quantitative justification for the application of life stage-specific adjustments for duration-specific health values (e.g., use of life stage-specific RfV for a specific duration of exposure) if the assessment warrants it.

5.1.1. Hazard Characterization

This section includes the integrative summary of information on the capacity of an environmental agent to cause adverse effects in laboratory animals and humans at different life stages. The qualitative description is based both on the type of data and quality of data derived from humans and laboratory animals and on the integration of ancillary data (e.g., structure activity analyses, genetic toxicity, TK, TD, and MOA) into a WOE narrative. Tables 5-1 through 5-3 are not intended to be proscriptive but are provided to assist the preparation of the narrative.

5.1.2. Dose-Response Characterization

The dose-response characterization focuses on quantitative relationships between exposure (dose) and effects. Critical outcomes and life stages of concern from the hazard characterization are examined quantitatively and summarized in this section. For outputs of this analysis to be useful in benefits analysis, the endpoints that are quantified must be expressed as changes in adverse outcomes (e.g., change in incidence of illness or symptoms) that are readily understood and perceptible by the public. Methods for assessing dose-response relationships often depend on assumptions used in the absence of data. These approaches can strongly influence the overall assessment; thus, assumptions need to be clearly articulated in the risk characterization section.

5.1.3. Exposure Characterization

The exposure characterization includes a narrative describing the basis for values used in exposure scenarios. If the values are based on data, then the quality, purpose, and representativeness of the database should be described. Alternatively, if they are based on assumptions, the sources and general logic used to develop the assumptions should be described. The major factors thought to account for the greatest uncertainty in the exposure assessment should be described and linked to information from sensitivity analyses or lack of particular data.

Table 5-1. Issues Addressed in Hazard Characterization (Section 4.1.)

Toxicological Evidence	What are the key toxicological studies that provide the basis for health concerns following children's exposures? To what degree do key studies meet data quality objectives (U.S. EPA, 2002b)? Are the data from laboratory animals or human studies? In a single or multiple species? What adverse outcomes at the lowest exposure levels were observed, and what is the basis for these observed outcomes? Have precursor events been identified? Was dosing/exposure during potential or known critical windows of exposure identified? Is there intraspecies concordance of effects? Are all studies supporting these findings discussed, and do any valid studies contradict these findings? Besides the developmental life stage effects observed in the key studies, are there other health outcomes of concern? Are negative toxicological studies (data) considered in the hazard characterization? What are the significant data gaps? Do the cited studies include data relevant to humans? In the case of animal study data, what is known about the comparative developmental life stages of exposure in humans? Are the routes of exposure relevant to humans? Is there concordance of effects between animals and humans? If not, are there underlying biological reasons to explain these differences?

Human Evidence	What human data are available? What types of studies are available (e.g., case-control, cohort or human ecologic studies, or case reports or series)? To what degree were exposures described (e.g., the exposure level and the life stage of exposure)? To what degree were confounding factors, effect modifiers, and other risk factors considered? What were the major demographic and other personal/community characteristics examined (e.g., age, sex, ethnic group, socioeconomic status, smoking status, occupational exposure)? Were the findings examined for biologic plausibility, internal and external consistency, and the influence of limitations of the design, data sources, and analytic methods? Are "negative" human studies (data) considered in the hazard characterization? Did included studies have sufficient power for confidence in the results?
Mode of Action (MOA)	What were the relevant studies of MOA and toxicokinetics? How much is known about how (through what biological mechanism or MOA) the chemical produces adverse effects? Does this MOA information aid in the interpretation of the hazard data for different life stages? What are the implications of specified MOAs for potential adverse effects and their relationship to risk?
Weight of Evidence (WOE):	What is the confidence in the conclusions? Are there alternative conclusions that are also supported by the data? Are there significant data gaps? How do these impact the magnitude of uncertainty in the assessment? What are the identified uncertainties? What are the major assumptions? What is the relevance of animal studies to humans at particular life stages?

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Table 5-2. Issues Addressed in Dose-Response Characterization (Section 4.2.)

Nature and Extent of the Database:	What data were used to develop the dose-response curve? Would the results have been significantly different if based on a different data set? Were there differences in the dose-response curves for different life stages? If *laboratory animal* data were used, consider the following: Which species were used? Was it the most sensitive species, the average of all species, or another species? Were any studies excluded? Why? If *human data* were used, consider the following: Which studies were used? Were they only positive studies, all studies, or some other combination? Were any studies excluded? Why? Was a meta-analysis performed to combine epidemiological studies? What approach was used?
Dose-Response Curve	Was a model used to develop the dose-response curve and, if so, which one? What rationale supports this choice? Is chemical-specific information available to support this approach? Is life stage-specific information available for modeling? What other models were considered? How was the benchmark response chosen? How were the benchmark doses (BMDs) determined? Were the life stage data applied appropriately to different duration BMDs? What assumptions and uncertainty factors were used? Did these appropriately account for life stage information or data gaps? How were the slope factors derived? How were life stage issues incorporated into the assessment? What were the results of uncertainty analyses? What were the results of sensitivity analyses? Were data needs identified from either uncertainty or sensitivity analyses? What is the confidence in the risk estimates?

Expected Exposures	Discuss the route, level, timing (i.e., life stage), and duration of exposure used in the 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 toxicokinetic data available to extrapolate across routes of exposure? Are data available from the same life stages as the expected exposed human populations? If not, are toxicokinetic data available to extrapolate across life stages? 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., the margin of exposure? One to two orders of magnitude? Multiple orders of magnitude? What is the impact of such an extrapolation?

1 **Table 5-3. Issues Addressed in Exposure Characterization (Section 4.3.)**

Pathways of Exposure	What are the most significant pathways of environmental exposure? What are the likely routes of exposure?
Sources of Exposure	What are the most significant sources of environmental exposure? Are there data on pathways of exposure from different media? What is the relative contribution of different pathways of exposure? What are the most significant environmental pathways for exposure?
Populations	Describe the groups assessed, including parents before conception, and different developmental life stages (e.g., pregnant women, infants, young children, adolescents, highly exposed groups of children, and highly susceptible groups of children).
Time Frame of Exposure	Describe the time frame of exposure, including pattern (continuous, intermittent) and duration of exposure (acute, short term, subchronic, or chronic).
Location of Exposure	Discuss locations where children are being exposed (e.g., residence, school, outdoors).
Activities Leading To Exposure	Discuss activities that result in significant exposures (e.g., breastfeeding, mouthing, sports, and after-school employment).

Exposure Characterization	Describe the basis for the exposure assessment, including any monitoring, modeling, or other analyses of exposure distributions. What are the key descriptors of exposure? Describe the range of exposures for the various categories of individuals (e.g., "average" individuals, the most highly exposed individuals, the general population, children, aged, males, and pregnant or lactating females). 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? Is there information on highly exposed subgroups? Who are they? What are their levels of exposure? How are they accounted for in the assessment?
Cumulative and Multiple Exposures	Is there reason to be concerned about cumulative or multiple exposures to classes of agents with a similar mechanism or mode of action? Are there biological, behavioral, ethnic, racial, or socioeconomic factors that may affect exposures?
Exposure Conclusions	Summarize exposure conclusions, including the following: What are the results of different approaches (i.e., modeling, monitoring, and probability distributions)? What are the life stage-specific exposures and ranges of exposure? What are the limitations of each exposure assessment methodology and the range of the most reasonable values? What is the confidence in the results obtained and the limitations of the results? What were the results of uncertainty analyses? What were the results of sensitivity analyses? Were data needs identified from either uncertainty or sensitivity analyses?

5.2. SUMMARY OF ALL THE VARIABILITY AND UNCERTAINTY ANALYSES

Determine whether different approaches used to estimate exposure or health outcome provide similar risk estimates. Information from different sources can carry different kinds of

variability and uncertainty. Knowledge of these sources of variability and uncertainty are important when considering integration of the uncertainties in the risk characterization. This knowledge can have an impact on decisions that must be made about the need to acquire more data/knowledge to reduce these uncertainties. This summary includes clear and concise statements about the limitations of the risk assessment and may include discussion of uncertainties in other related assessments. Critical data gaps, defined by the impact they have on the risk assessment, should be identified and described. These critical data gaps and the attendant research needs may provide insight into future reductions in uncertainties in risk assessment

Table 5-4. Issues Addressed in Variability and Uncertainty Analyses

Variability and Uncertainty Analyses	Does the assessment capture the variability in the exposed population? What are the uncertainties in the assessment for different life stages of development? What are the limitations of the data available? What data gaps exist? What are the priority data needs for reducing uncertainties? How can additional data reduce uncertainties in life stage-specific risk assessment?

5.3. RISK CONTEXT

The risk characterization must be presented in a context that relates to the original problem identified in the planning and scoping phase of the framework. Risk assessment is an iterative process that grows in depth and scope; this occurs in stages, from screening for priority making, to preliminary estimation of risk, to fuller examination in support complex regulatory decisions. If the statement of the problem evolved during the analyses, this process needs to be summarized. The risk context of major conclusions and strengths of the assessment in each of the three main phases of the analyses (i.e., hazard characterization, quantitative dose-response, and exposure assessment) should be discussed along with the major limitations and uncertainties. This summary should include what the decision makers and the public need to know about the

key conclusions and assumptions and a balance between confidence and uncertainty in the assessment.

Table 5-5. Types Of Issues To Be Considered to Illustrate The Risk Context

Risk Context	What are the science policy assumptions in each of the three major components of the analyses? What are the alternative approaches evaluated? What are the reasons for the choices made? What are the qualitative characteristics of the hazard to children (e.g., voluntary vs. involuntary, technological vs. natural.)? (*Comment on findings, if any, from studies of risk perception that relate to this hazard or similar hazards.)* How do life stage-specific risks compare? How does this risk compare with other risks in this regulatory program, or other similar risks that EPA has evaluated? How can benefit analysis utilize the information derived from the risk characterization? Where appropriate, can this risk be compared with other risks characterized by EPA, characterized risks by other federal or state agencies, or common risks with which people may be familiar? What are the limitations of making these comparisons? Are there significant community concerns that influence public perception of risk?
Existing Risk Information	Comment on other risk assessments that have included consideration of health risks from children's exposures on this chemical by EPA, other federal agencies, or other organizations. Are there significantly different conclusions that merit discussion?
Other Information	Is there other information that would be useful to the risk manager or the public in this situation that has not been described above?

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

This report summarizes the process for assessing health risks resulting from children's exposure to environmental agents using a phased approach that includes problem formulation, analysis, and risk characterization. It utilizes EPA documents that have outlined a similar approach (U.S. EPA, 1998a, 2003a) as well as the report of a workshop (ILSI, 2003) that formed the basis for a children's health risk assessment framework. The approach here is not to provide guidance per se, but rather, using the existing framework approach, to pose targeted questions to address each phase of the process. In addition, the report references appropriate guidelines, guidance documents, and other relevant reports and literature that can be drawn upon for more detailed information.

As indicated in this report, several EPA risk assessment guidelines relate to health risks from children's exposures. The most relevant are the developmental toxicity risk assessment guidelines (U.S. EPA, 1991) that deal with the whole organism during development, but focus primarily on the effects of prenatal exposures and, to a limited extent, on postnatal exposures and outcomes. Other guidelines/guidance are focused on system- or disease-specific issues that include the effects of developmental exposures, e.g., reproductive toxicity (U.S. EPA, 1996), neurotoxicity (U.S. EPA, 1998b), or cancer (U.S. EPA, 2005b, 2005c). 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, TK, or genomics data) are lacking.

The relevance of specific developmental outcomes for application to risk assessments for various durations of exposure (i.e., acute, short term, longer term, and chronic) has not been generally defined, although this issue is considered in many of the risk assessments currently being generated across EPA. Gaps identified in the document *A Review of the Reference Dose and Reference Concentration Processes* regarding data needs and alternative approaches and strategies for developing testing guidelines are still necessary (U.S. EPA, 2002b, Section 5). In addition, there has not been a focused guidance document on dose-response assessment with developmental exposures, despite the fact that a good deal of research and methods development on BMD (U.S. EPA, 2000a) and pharmacokinetic modeling (e.g., Clewell et al. 2002a; Ginsberg et al. 2004b) has been done using developmental data in animals and humans.

With regard to exposure assessment, there is very little guidance on approaches specific to children at different life stages, except for *Child Specific Exposure Factor Handbook* (U.S. EPA, 2002a) and the guidance on selecting appropriate age groups for assessing childhood exposures (U.S. EPA, 2003b). Much more is needed on methods for both screening level and more detailed quantitative estimates of children's exposures. Data for exposure factors determinations for all the recommended age groups are limited or nonexistent for some exposure factors.

Finally, one issue addressed briefly in this report is the integration of toxicity data and children's exposure estimates, an issue for which essentially no guidance exists. Because the age groupings of concern for exposure and susceptibility to environmental agents can differ significantly, guidance is needed on using information on biological processes underlying development, MOA information, chemical-specific mechanisms, anatomical, physiological, and behavioral characteristics at different developmental life stages 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. Some of these questions are:

- How can adult biomonitoring data be applied to children?
- How can biomonitoring data be interpreted to characterize exposure?
- How can data from children be interpreted across developmental stage?
- How can activity pattern data be used to classify children for exposure assessment?

Many of these questions are actively being investigated. These efforts will likely contribute to future guidance and policy papers on specific issues. However this framework attempts only to outline the issues these issues and does not attempt to predict outcome or positions.

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.

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.

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 of interest. This association between the exposure of interest and the confounder (a true risk factor for disease) may make it falsely appear that the exposure of interest is associated with disease.

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.

Detoxificaton – Process, or 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 should reflect the biologically active form of the chemical, its level, and duration of exposure, as well as 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 – Process of measuring or estimating dose.

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 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 (e.g., 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, life stages, 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, 2005b, 2005c). Toxicokinetic and toxicodynamic steps that lead to a toxic response can be considered as key event(s).

Life Stage Approach – The comparison of exposure and effect data across different life stages 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 result 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 non-cancer 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.

(Durations include acute, short term, longer term, and chronic and are defined individually in this glossary.)

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 2001a).

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., life stage, demographic feature, or genetic characteristic).

Susceptible Subgroups – May refer to life stages, 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 somewhat 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.

Toxicodynamics (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.

Toxicokinetics (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 *1)* variation in susceptibility among the members of the human population (i.e., interindividual or intraspecies variability); *2)* uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); *3)* uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); *4)* uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and *5)* 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 sub-populations 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 life stage 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 should be 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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APPENDIX 1. HAZARD CHARACTERIZATION – EXAMPLE QUESTIONS FOR THE DATA EVALUATION OF INDIVIDUAL STUDIES

Topic/Subject (Section)	Study Type	General Questions	Life-Stage Specific Questions
Study Purpose (4.1.3.1.)	All Studies	►What was the purpose of the study? Was the study testing a hypothesis? ►Was the study conducted in response to a public health concern?	►Were life-stage-specific exposures and associated outcomes addressed in the study?
Study Design (4.1.3.2.)	All Studies	►What was the study design (e.g., cross-sectional, longitudinal, multigenerational)?	►What life stages were represented in the study (for both exposure and outcome)? Do the representative life stages include developmental life stages?
		►What were the study protocol, exposure paradigm, exposure timing, exposure frequency, and outcomes assessed?	►Did the study methods address specific life stages? If so, how?
	Human Studies	►What were the sources of data for exposure, health outcome, and risk factors/confounders/effect modifiers? What were the strengths and limitations?	►Did the available studies assess exposures during development?
		►What methods were used to control, measure, or reduce various forms of potential error (e.g., selection bias, misclassification bias) and their potential impact on the findings? Does this impact the validity and reliability of the methods used to determine exposure and outcome? If so, how? What were the response rates?	►How do the methods impact the validity and reliability to determine children's exposure and outcome?
		►What demographic and other personal/host factors were examined? ►Were potential confounders and effect modifiers examined and adjusted for, where appropriate?	►How was life stage/age measured (this is particularly important for gestation exposures)? ►Were other life stage factors important for the outcomes and exposures assessed?
		►Was a biological explanation of the findings proposed? If so, were the findings examined for biological plausibility, internal and external consistency of findings, and the influence of limitations of design, data sources, and analytic methods?	►Were biological plausibility, internal and external consistency of findings, and limitations considered for life stage-specific data?

Topic/Subject (Section)	Study Type	General Questions	Life-Stage Specific Questions
	Animal Studies	►Was the study conducted in accordance with good laboratory practices?	►Were life stage -specific studies conducted in accordance with good laboratory practice?
		►Were appropriate analytical techniques used to measure the stability, homogeneity, and actual dose level of the test substance in the study (in the water, feed, air, etc.)? Was target dose assessed or modeled?	►Were perinatal doses assessed or modeled?
		►Were an appropriate number of animals used? Were both sexes examined, as appropriate? Were adequate sample sizes assessed for each outcome?	►For developmental outcomes, were adequate sample sizes assessed; were appropriate numbers of litters used; were both sexes considered as appropriate?
		►Were the dose range and levels appropriate? What was the basis for selecting doses? ►Was an appropriate method used to assign animals to dose or test groups?	►Were the dose range and levels appropriate across life stages evaluated? ►Was an appropriate method used to assign animals to dose or test groups at various life stages?
		►Was an appropriate route and matrix (e.g., vehicle, formulation, duration) of exposure employed?	►Was an appropriate route and matrix (e.g., vehicle, formulation, duration) of exposure employed across various life stages studied?
		►What were the animal species and strain used in the study? Is this the most relevant animal model and why?	►What is known about the sensitivity of this animal species and strain for the exposure and outcomes of concern? ►What is known about critical windows of exposure (e.g., developmental windows of susceptibility) or effect (e.g., latent expression of developmental toxicity) for the animal species and strain?

Topic/Subject (Section)	Study Type	General Questions	Life-Stage Specific Questions
Outcomes (4.1.3.4.)	All Studies	►Which outcomes were observed in the study? ►Were all appropriate outcomes assessed (as determined by toxicological information about the chemical, including mode of action (MOA), target organ toxicity, etc.)?	►At which life stages were outcomes assessed? Describe these outcomes. ► Were there outcomes in the study that occurred at different life stages? Which outcomes occurred during developmental stages and which occurred during adult stages? ►Were the outcomes life- stage dependent? ►Were there life stage-specific outcomes that should have been assessed, but were not?
		►Were methods of assessing outcomes appropriate and optimum (if not, state limitations)?	►Were methods to assess life stage-specific outcomes appropriate? ►Were methods to assess outcomes after exposures at different life stages appropriate? If not, what were any possible restrictions or errors in the methods of assessments used in the study?
		►What is known about the temporal relationship between exposure and outcome?	►Describe the outcomes for exposures at different life stages. Were outcomes dependent upon the exposures during critical stages of development?
		►Is there a known MOA? Are outcomes consistent with what is known about MOA?	►If there is a known MOA, is it relevant for life stages of exposure and the outcomes represented in the study, or would you expect the MOA to be different? Are there different MOAs suspected for different life stages? ►Are there inconsistencies between the outcome and the assumed MOA at different life stages? For the outcomes assessed, have precursor events been identified? If so, were precursor events similar across life stages?
		►Are author interpretations and conclusions supported by the data?	►Do the authors interpret the results of the study according to life stages or in a way that acknowledges differences in life stages? Do the authors make developmental stage-specific conclusions in the study? If so, describe. ►Are the author's assumptions and interpretations about life stage-specific results supported by the data?

Topic/Subject (Section)	Study Type	General Questions	Life-Stage Specific Questions
Study Exposures (4.1.3.3.)	All Studies	►What was the type (i.e., single or multiple chemicals), route and method of exposure(s)?	►Was the route the same throughout all life stages? ►Were the methods of exposure appropriate (i.e., relevant to the age-related exposure pathways) for the age groups exposed?
		►What was the exposure/dose concentration?	►Was the applied/target concentration (animal studies)/exposure/dose concentration validated or confirmed analytically? ►Did exposure occur across more than one developmental life stage(s) in the study? If so, which exposures/doses were assessed during specific stage(s) of development? ►Were the dose levels the same across all the life stage(s) identified in the study? If not, what were the exposure/dose level differences between different life stages? ►Were the differences attributable to factors at specific life stages (e.g., behavior or activities)? ►Were there developmental stage-specific behaviors 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?
	Human Studies	►What was the exposure source(s)?	► Was there more likely to be exposure(s) from this source during certain life stages than others? If so, would this be expected to affect the results of the study? Was this accounted for in the study?
		►Were other possible sources of exposure considered?	►Were other possible sources of exposure considered for various life stages?
	Animal Studies	►Was the duration of exposure adequate and relevant for the study?	►Did the exposure interval cover different life stages, partially or completely? ►Was exposure verified for critical life stages?
Toxicokinetics (4.1.3.5.)	All Studies	►Are there available toxicokinetic (TK) data?	►Are there TK data for the specific life stage(s) assessed in the study? ►Are there life stage-specific differences

Topic/Subject (Section)	Study Type	General Questions	Life-Stage Specific Questions
			in toxification/ or detoxification?
	Animal Studies	►Were possible alterations in metabolism considered at the higher exposure/dose levels?	►Are there data to suggest life stage-specific metabolic differences at the higher exposures/doses?
Toxicodynamics (4.1.3.6.)	All Studies	►Are there available toxicodynamic (TD) data?	►Are there any life stage-specific TD data?
		►What is known about the MOA for the toxicant?	►Are MOA data known for other life stages and outcomes relevant to the life stages of concern in this study?
Qualitative Dose-Response (4.1.3.7.)	All Studies	►What is the dose-response relationship for adverse outcomes?	►Are there life stage-specific dose-response relationships? Do they vary by life stage?
Uncertainties (4.1.3.8.)	All Studies	►Are there data gaps or inadequacies in the study protocol or methodologies that lead to uncertainties in the evaluation of the study?	►Are any of these data gaps or uncertainty considerations life stage-specific, i.e., were some life stages assessed, while and others were not? ►Were critical windows of exposure and associated outcomes adequately addressed?
		►Are there any data or other information that are critical to the evaluation of the study that were not included or not fully reported?	►Were these inadequacies in data presentation specific to critical life stages or windows of exposure?
		►Are there data or analyses that are inconclusive?	►Were there inconclusive data analyses for the interpretation of outcomes for specific life stages?
Summarizing the Hazard Database (4.1.4.1)	All Studies	►What pathways (including media and route) of exposure were covered in the studies?	►What intervals of exposure were examined? ►Are they pathways of exposure relevant to children?
		►What intervals of exposure were examined?	►Did these exposure intervals include all relevant life stages?
		►What outcomes were observed?	►Do the data provide information about the susceptibility of children at specific life stages? Is the relationship consistent across life stages?
		►What is the relationship among the different outcomes (i.e., what is the pattern of outcomes observed)?	►Have the appropriate studies been performed (within the database or elsewhere) to determine critical windows of exposure (Selevan et al. 2000)? If so,

Topic/Subject (Section)	Study Type	General Questions	Life-Stage Specific Questions
			what are they? Did exposure intervals include known or suspected critical windows? ►Does the pattern of outcomes suggest a syndrome?
Uncertainties, Gaps, and Variabilites in the Database (4.1.4.2.4)	All studies	►What are the data gaps for exposure?	►Which life stages of exposure were assessed? Were all life stage-relevant exposure intervals evaluated? Did exposure occur throughout all critical life stages? Were there developmental stages during which exposure was intermittent or did not occur, and what was the potential impact of these gaps in exposure? ►Were all life stage-relevant pathways of exposure evaluated? Are there toxicokinetic data that support the study design and the interpretation of the data for critical life stages? ►Are there additional exposures beyond those present that might provide additional information relevant to children's health risk assessment? ►Were life stage-appropriate biomarkers of exposure assessed?
		►What are the data gaps for outcome?	►Were all critical outcomes (both broad screening level and chemical- or MOA-specific outcomes) evaluated across life stages? For example, have appropriate organ systems, tissues, and outcomes been adequately assessed for all life stages of concern? ►Were life stage-appropriate biomarkers of outcome assessed?

Topic/Subject (Section)	Study Type	General Questions	Life-Stage Specific Questions
		►What uncertainties have been identified? ►Did the conduct of the study result in uncertainties in study results or data interpretation? Do some studies or data need to be excluded on the basis of poor quality? ►Can information from the comparison of structurally related chemicals, or chemicals with a similar MOA, be used to modify the impact of identified uncertainties or data gaps?	►Have any uncertainties specific to the assessment of risk to children's health been identified? ►Did the conduct of the study result in uncertainties in study results that are particularly pertinent to children's health risk assessment or life stage-specific data interpretation? Do some studies or data need to be excluded on the basis of poor quality? ►Can information from the comparison of structurally related chemicals, or chemicals with a similar MOA, be used to modify the impact of identified uncertainties or data gaps for life stage-specific data?

Topic/Subject (Section)	Study Type	General Questions	Life-Stage Specific Questions
Extent of the Database (4.1.4.2.5)	All Studies	►What is the extent of the database? ►What is the quality of the database? ►What is the quantity of the database (i.e., what studies were available for evaluation)? ►On what information is the characterization of the extent of the database established? How do the quality and quantity of the database affect the uncertainties and data gaps?	►What is the extent of the database for children's health risk assessment? ►What is the quality of life stage-specific data included in the database? ►What is the quantity of life stage-specific data in the database? ►Does the extent of the database for children's health hazards indicate the need for follow-up studies to better define uncertainties, e.g., for the specific assessment question and issues?