Guidance for the Preparation of a Twenty First Set Toxicological Profile

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

U.S. PUBLIC HEALTH SERVICE

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CONTENTS

GENERAL

These guidelines are designed to assist authors and chemical managers with preparing toxicological profiles for the Agency for Toxic Substances and Disease Registry (ATSDR). A list of abbreviations and acronyms used throughout this guidance document appears in Attachment B.

PURPOSE AND SCOPE OF THE ATSDR TOXICOLOGICAL PROFILES

The toxicological profiles are summaries of ATSDR's evaluations concerning whether and at what levels of exposure adverse health effects occur and levels at which no adverse effects occur. The profiles include information about exposure and environmental fate that may help readers determine the significance of levels found in the environment. The primary users of these documents are expected to be the informed public and health professionals who need succinct interpretations of toxicological data for such purposes as responding to telephone inquiries from the public and assessing a specific problem at a Superfund site, among others.

Toxicological profiles provide interpretations of data, which distinguishes them from ordinary reviews. Interpretations are useful for those health professionals who may not have the resources to gather and consider all the toxicological data themselves.

Interpreting data often requires judgment and implicit assumptions that are more a matter of policy than objective science. Specifically, the profiles incorporate ATSDR's evaluations of the validity of particular studies and the inferences that can be made from them. To this end, the profiles do not provide all the information necessary to support these evaluations; presenting data in sufficient detail to allow users to weigh all the evidence themselves is incompatible with the concept of a "profile." Nor do the profiles present detail on selected studies (except as noted in this document), because the absence of a discussion of other studies would not allow users to form independent judgments of the meaning of the data.

QUALITY CRITERIA FOR ANIMAL AND HUMAN STUDIES

ATSDR has adopted the National Research Council's (NRC's) "Guidelines for Assessing the Quality of Individual Studies," which appear in *TOXICITY TESTING: Strategies To Determine Needs and Priorities,* published by NRC in 1984. ATSDR agrees with the NRC that judging the quality of past and future studies solely by today's standards is inappropriate. The NRC considers a report of scientific findings adequate for use in health hazard assessment if the report meets the following basic criteria (refer to Attachment C).

- All elements of exposure are clearly described.

- Results in test subjects are predictive of human response, and test subjects are sensitive to the effects of the substance.

- Controls are comparable with test subjects in all respects except the treatment variable.

- End points answer the specific questions addressed in the study, and observed effects are sufficient in number or degree to establish a dose-response relationship that can be used in estimating the hazard to the target species.

- Both the design and the interpretation of the study allow for appropriate statistical analysis of the data.

Where appropriate, these criteria should be applied to judgments on the quality of data from epidemiological investigations and other scientific studies of relevance to ATSDR's toxicological profiles.

The reliability of epidemiological data in hazard identification is increased when results are obtained from studies that have the following characteristics (refer to Attachment D).

- Are derived from well-designed and well-executed case control or cohort studies that are free from bias.

- Display a strong association unlikely to be due to chance variation.

- Follow a logical, temporal sequence of exposure-response.
- Have been replicated in a variety of settings.
- Exhibit a dose-response relationship, using valid estimates of exposure and dose.
- Are toxicologically plausible.
- Where possible, include an examination of causality.

In addition, ATSDR recognizes the following desirable factors of studies or reports of scientific findings as set forth in the NRC guidelines:

- Subjective elements should be minimized.
- Peer review of scientific papers and of reports is desirable. *Note: The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) mandates the peer review of toxicologic testing results that ATSDR uses.*
- Results reported have increased credibility if they are supported by findings from other investigations.
- Similarity of results to those of tests conducted on structurally related compounds increases scientific confidence.
- Evidence of adherence to good laboratory practices improves confidence in results.

GENERAL GUIDANCE FOR PREPARING A TOXICOLOGICAL PROFILE

When preparing a toxicological profile, avoid describing studies, with two exceptions.

- A brief description is required of the studies that provide no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs) for each effect included in a level of significant exposure (LSE) table.

- If a conclusion is uncertain or controversial, a brief description of the studies that are the basis for the uncertainty may be included. Description should be limited to those factors that are necessary to summarize the issue; do not include all the details of the study.

Consider all data when making conclusions. ***Support all conclusions with references to original literature, not reviews. Refer to an abstract only if the original paper is not obtainable. Current abstracts should be discussed in the "Ongoing Studies" sections of Chapters 3, 6, and 7. Older abstracts should be disregarded if not followed up in the literature.***

Refuting studies that contradict conclusions made in the profile is unnecessary. Such studies should, however, be acknowledged in the text and listed in the reference list. This will aid readers who have the resources and inclination to investigate the subject in greater depth, while not distracting the primary audience for which the profile is written. You may choose to present a succinct justification of your conclusion if it differs from what appears at first glance to be the overwhelming weight of evidence, but this option should be exercised rarely.

An individual designated by the contractor works with the designated ATSDR representative to obtain epidemiological studies, health surveys, and current chemical regulations and guidelines from state health departments.

An individual designated by the contractor works with the designated ATSDR representative to obtain information on U.S. Environmental Protection Agency (EPA) sponsored research using a list of EPA employees/contractors and their respective chemical-specific research (to be

provided by ATSDR/EPA). This information is compiled during a telephone survey and is used in the preparation of Chapters 3 and 8.

A general outline for the profiles is provided in Exhibit 1. Note the following:

The following bullets have been amended from the original:

- The outline presented in Exhibit 1 lists the topics that should be included in every toxicological profile. It follows the organization of the table of contents for toxicological profiles but does not match the Table of Contents exactly. Specifically, the outline contains some subheadings that do not appear in the Table of Contents.

- The phrase "ATSDR boilerplate" denotes a heading or text that must be included in every toxicological profile, even if information on the topic does not exist. (In that case, the boilerplate headings or text should be followed by a statement indicating that information on the topic does not exist.) All such required material is provided in this guidance document and the attached exhibits, and in the WordPerfect templates that have been created to facilitate development of the profiles (see the editorial guidelines that follow). Boilerplate material is presented in a bold type to distinguish it from guidance information.

- The term "DUMMY" denotes a heading that can be included in a toxicological profile if information on the topic exists. If the information can be incorporated into an already existing section of the document, it should be. If the information does not readily fit into an existing section, then the dummy heading can be added to accommodate the information.

As noted above, this guidance document contains both guidance information and boilerplate material. Although some section titles in this document match the boilerplate titles used in toxicological profiles, others do notCeither because they address more than one profile subsection or because they represent more general guidance.

FRONT MATTER

The front matter of the profile contains, in order, the following:

-Title Page (Exhibits 3 and 4)
-Disclaimer (Exhibit 5)
-Update Statement (Exhibit 5a)
-Foreword (Exhibit 6)
-Quick Reference for Health Care Providers (Exhibit 5b)
-Contributors (Exhibit 6a)
-Peer Review (Exhibit 6b)
-Contents (Exhibit 7)
-List of Figures (Exhibit 8)
-List of Tables (Exhibit 9)

CHAPTER 1. PUBLIC HEALTH STATEMENT

Chapter 1 of the toxicological profile, if removed from the rest of the document, should still communicate to the lay public essential information about the substance. This chapter is intended to be a health effects summary written in layperson's, with the audience being the general public, especially people living in the vicinity of a hazardous waste site or substance release. Technical terminology should be avoided. Definitions of all common scientific, toxicologic, medical, and epidemiologic terms should be provided in the text. Statements should include references during the development stage but they should be deleted from the camera-ready final.

The Public Health Statement (PHS) should be written at the reading level of a daily newspaper, avoiding technical terms in Attachment E of this guidance document. If technical terms are used, they should be defined in the text. Whenever appropriate, the PHS should be written in the second person and in the active voice. Aim for a readability level in the "good" range (8th to 10th grade) from the Right Writer printout. *Note: The name of the substance, synonyms, and trade names (presented in Section 1.1) should be added to the Right Writer dictionary before running the program.*

The tone of this chapter should be factual rather than judgmental. Terms and units should be used consistently throughout this chapter. Where possible, use parts per million (ppm). Define units the first time they are used, e.g., one part of [substance x] in a million parts of water (ppm).

The following units of measure can be used when reporting environmental data, when describing reliable human health data, or when providing recommended exposure limits:

Gas or vapor:	ppm
Particulate:	mg/m^3
Food:	ppm
Water:	ppm

Other units of measure can be used if justifiable. Select units of measure that permit the use of whole numbers.

Major headings for this chapter are in question format. The answer to each question should include a sentence directing the reader to chapters in the profile that provide more information on the given topic.

The following "boilerplate" language provided by ATSDR is to precede Section 1.1. Although this boilerplate will be sufficient for most profiles that discuss a single substance, it may require some modification for profiles covering more than one form, compound, or radionuclide. In addition, if more than one map is presented in Chapter 6, the boilerplate will also require modification.

> **This public health statement tells you about [substance x] and the effects of exposure. The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in federal cleanup activities. [Substance x] has been found in at least [number of sites] of the 1,613 current or former NPL sites. However, the total number of NPL sites evaluated for [this, these] [substance, substances] is not known. As more sites are evaluated, the sites at which [substance x] is found may increase. This information is important because exposure to [this, these] [substance, substances] may harm you and because these sites may be sources of exposure.**
>
> **When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance or by skin contact.**
>
> **If you are exposed to [substance x], many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you**

come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

Within each section of the PHS, information should be presented in an order that is clear, concise, and logical. The guidance provides examples of specific material that should be considered and discussed (if relevant) in each section. The discussion need not be limited to the material requested.

1.1 WHAT IS [SUBSTANCE X]?

Introduce common synonyms and trade names for [substance x]. If the profile covers more than one substance (e.g., DDT, DDE, DDD), discuss the different forms using lay terms. For profiles in which the title covers more than one substance but only selected substances are discussed, it should be clear to the reader which forms are discussed and why others are excluded. Discuss which forms are most likely to be found in the environment, especially near hazardous waste sites. Example: "Pure arsenic is a gray, metal-like material, but this form is not common in the environment. Rather, arsenic is usually found . . . ." Provide a physical description (e.g., color, physical state, volatility, flammability) of the chemical. Chemical reactivity should be included for substances that have high reactivities with water, air, or other common substances. Again, the discussion should emphasize the forms that are commonly found in the environment.

Describe how the substance smells and/or tastes. Distinguish between differences in perception of odor and taste at low concentrations and high concentrations. If a substance is without a characteristic odor or taste, state this. The odor and taste threshold should be included here and the units defined, e.g., "Most people begin to smell benzene in air at 2 to 5 parts benzene per million parts of air (ppm). Most people begin to taste benzene in water at 1 to 5 ppm." What are the major natural and man-made sources of the substance? Does it occur naturally? If so, where, when, or from what? Is the substance manufactured or mined? If so, from what? Indicate if the substance has a high production volume, e.g., "Benzene ranks in the top 20 in production volumes for substances produced in the United States." If the substance is no longer produced, state when production was terminated. If the substance is a contaminant and not

intentionally produced, identify the conditions under which it forms (both natural and anthropogenic) and the substances in which it is found. Identify the common uses of the chemical. Is it a final product, an intermediate, or is it formulated into something else (e.g., a pesticide)? For high production substances, it is important to indicate whether most of the substance produced is used to make other substances. Example: "Most of the vinyl chloride produced in the United States is used to make polyvinyl chloride (PVC). PVC is used to make a variety of plastic products, including . . . ." If the substance is no longer used, provide information regarding its previous uses. Refer the reader to the Chapters 4 and 5, where further information can be found.

1.2 WHAT HAPPENS TO [SUBSTANCE X] WHEN IT ENTERS THE ENVIRONMENT?

Describe the ways in which the substance can enter the environment. (Do not discuss exposure here.) Include atmospheric emissions, discharge into waterways, accidental spills, and leaks from storage and waste sites. Discuss factors that determine the fate of a substance once it is released into the environment. These factors should include physical-chemical properties (e.g., solubility, volatility, and sorption). How does it move once it enters the environment? How quickly and easily can it move through soil (e.g., does the substance bind tightly to soil or does it move freely through soil)? Where relevant, indicate that movement in soil depends on the type and condition of the soil and other environmental factors.

Discuss how long the substance persists in different environmental media (e.g., days, weeks, years). Do transformation and degradation occur? Are any of the degradation products toxic? If so, do they pose a threat to humans? When presenting information on persistence of a substance in environmental media such as water or soil, use field studies or other relevant studies. Be aware that the information from laboratory studies conducted under ideal conditions (e.g., select microbial population, elevated temperature) may misrepresent actual persistence. What is the substance's potential for bioaccumulation and biomagnification in aquatic and terrestrial biota? Refer the reader to Chapters 5 and 6, where further information can be found.

1.3 HOW MIGHT I BE EXPOSED TO [SUBSTANCE X]?

This section should be consistent with information in Chapter 2 (Relevance to Public Health) and Chapter 6. Discuss potential sources of exposure, including common and uncommon sources (e.g., breast milk, soil). Provide some perspective, when possible, on the likelihood of exposure resulting from different sources of contamination. Indicate which human exposure pathways are expected to be the most significant at Superfund sites. Discuss the most probable routes of exposure for the general population, people living around waste sites and/or manufacturing, processing, or storage facilities, and people who work with or around [substance x]. Statements like "Most people are exposed to very low levels of [substance x]," if indeed true, can be included to indicate the extent of exposure to the general population. These general statements should be elaborated on by explaining why this is the case and how exposure occurs. Discuss how and by what means exposure to higher concentrations may occur.

For volatile organic compounds (VOCs), assess the importance of inhalation and dermal exposure from contaminated potable water. Example: "Leakage from underground gasoline storage tanks or from landfills and hazardous waste sites containing benzene can result in benzene contamination of well water. People with benzene-contaminated tap water can be exposed from drinking the water or eating foods prepared with the water. In addition, exposure can result from breathing in benzene while showering, bathing, or cooking with contaminated water."

Include background levels in different environmental media, e.g., groundwater, surface water, soil, air (indoor and outdoor), and food. When presenting data, use averages or ranges; avoid using median values. State the frequency of occurrence of [substance x] in different environmental media, e.g., [substance x] was detected in 5% of the wells that were monitored. If no data exist, state that. When known, provide an estimate or range of typical daily human intake of [substance x] from these sources. Do not report levels from NPL sites and highly contaminated areas as background levels, since these are often from isolated samples and may not be representative of levels to which humans are exposed.

What are occupational sources of exposure? Where extensive information exists, tables or bullets can be used to list occupational sources of exposure, occupations that may involve exposure, and/or situations in which people might be exposed to higher-than-normal levels of the substance. Include the number of people estimated to be exposed to [substance x] in occupational settings (see Section 6.5 of guidance). In some cases, not all occupations (and hence workers) are covered in the survey; in these cases, indicate other occupations that involve exposure but are not included in the estimated numbers. Refer the reader to Chapter 6, where further information can be found.

1.4 HOW CAN [SUBSTANCE X] ENTER AND LEAVE MY BODY?

Explain the three major routes of uptake (ingestion, inhalation, and dermal exposure), the relative rate and extent (e.g., "rapidly and completely") of uptake by each route, and the major factors that affect uptake (e.g., duration of exposure, level of exposure). Describe what happens to the substance after absorption. Is it metabolized to less harmful or more harmful products? If the compound is stored in the body for a long period, identify the major organs/tissues involved in storage. Discuss briefly how the substance is eliminated by the body; include excretion routes (e.g., urine, feces, breath) as well as relative time frames (e.g., quickly, slowly, hours, days). Refer the reader to Chapter 3 for further discussion.

1.5 HOW CAN [SUBSTANCE X] AFFECT MY HEALTH?

Insert the following boilerplate before the animal health effects discussion.

> **To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.**
>
> **One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get**

information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

The discussion in this section should give the lay reader an understanding of the essential exposure-duration-effect relationships that have been developed in the profile. Significant non-lethal effects at low and high doses should be represented if the data permit. The exposure-effect relationship discussed in the boilerplate to the PHS can be reemphasized here. When discussing health effects, state the medical terms, and define them in the text. Organize data by routes of exposure, and introduce data in order (i.e., inhalation, then oral, then dermal; acute exposure, then chronic exposure). Discuss human data before animal data. Distinguish between health effects associated with brief exposures and health effects associated with long-term exposures. Information from case studies, accidental poisonings, occupational and epidemiological studies, industrial accidents, and other data sources can be used when discussing health effects. Give a general description of all health effects. Actual levels or ranges and durations of human exposure should be used when the data are believed to be reliable.

Be careful of the wording when describing adverse health effects or presenting data; do not give the impression that everyone exposed experienced adverse health effects. Data can be presented by using descriptive ratios or general terms like "some," "few," "most," or "all." If sufficient human data exist to allow for a discussion of effects for a specific route and duration of exposure, do not present animal data. Any limitations to the human studies should be discussed. Where human data are lacking and health effects are unknown, this should be stated. Animal data can be used to support weak human data and in situations where human data do not exist. Include the species in which the effects were observed. Use qualitative terms when describing levels and durations of exposure from animal studies, and be consistent when using these terms. Distinguish between effects that have been observed in humans and those that have been observed only in animals. Where relevant, include statements of "effect not known" if there is no information.

The discussion of health effects should identify the major health effects of [substance x] (e.g., immunological, neurological, reproductive, major organ impairment). Report if the substance is known or not known to cause birth defects and/or reproductive effects (infertility) in humans or animals. Information should be provided where differences in the effects of the substance on males and females are well documented. Include exposures in the text that are associated with effects other than health (e.g., odor or taste threshold can be mentioned again). Have health effects been reported for humans exposed at levels close to the odor or taste threshold? If the data in Chapter 3 clearly show that certain individuals or populations are more susceptible to the adverse effects of the substance, this information should be provided. If relevant, information on hypersensitivity and allergic reactions should be discussed. When describing human health effects at specific levels, refer readers to Sections 1.3 and 6.4 for information on typical ambient levels. Consider whether these ambient levels are relevant to effect levels, and, if so, state this relevance to the general population and to populations exposed to higher levels. Example: "Most of the data on long-term exposure to benzene are from studies of workers employed in industries that make or use benzene. These workers were exposed to levels of benzene in air far greater than the levels normally encountered by the general population. Current levels of benzene in workplace air are much lower than in the past. Because of this reduction, far fewer workers have symptoms from benzene exposure."

If the substance has beneficial effects or is an essential or a normal constituent of human biochemical processes, this should be discussed. If the substance is essential, the recommended dietary allowance should be provided. Where relevant, distinguish between different forms of the compound associated with beneficial and adverse health effects.

Discuss the carcinogenic effects of the substance descriptively. If epidemiological or case studies show a strong link between exposure and cancer in humans, these studies should be discussed. Again, the text should be worded to indicate that exposure may increase the risk of an individual developing cancer and not that exposure is equated with cancer for all those exposed. Do not discuss cancer potency. Include the duration and levels of exposure, if known. Carcinogenic effects in animals should also be discussed including the organ systems affected. When discussing cancer effects in animals, qualitatively discuss the duration and levels of

exposure. If no human data exist, state so. If the data are not accepted by the National Toxicology Program (NTP), IARC, or EPA as showing a causal relationship, discuss the limitations.

If the substance has not been classified by the Department of Health and Human Services (DHHS), NTP, IARC, or EPA, state that the substance has not been classified for carcinogenic effects.

The discussion on cancer should be followed by the appropriate boilerplate statement for the carcinogenic classification of [substance x] as shown in the table below.

Order of agencies is:

1. DHHS (NTP)
2. IARC
3. EPA

Use the following wording, as appropriate:

Organization classification	Agency/Beginning of sentence	End of sentence
(N/A)	For DHHS (NTP) use:	**. . . is a known carcinogen**
(N/A)	**The Department of Health and Human Services has determined that [substance x] . . .**	**. . . may reasonably be anticipated to be a carcinogen.**
1	For IARC use:	**. . . is carcinogenic to humans.**
2a	**The International Agency for Research on Cancer has determined that [substance x] . . .**	**. . . is probably carcinogenic to humans.**
2b		**. . . is possibly carcinogenic to humans.**
3		**. . . is not classifiable as to its carcinogenicity to humans.**
4		**. . . is probably not carcinogenic to humans.**
A	For EPA use:	**. . . is a human carcinogen.**
B1 or B2		**. . . is a probable human**

	The Environmental Protection Agency has determined that [substance x] . . .	**carcinogen.**
C		**. . . is a possible human carcinogen.**
D		**. . . is not classifiable as to its human carcinogenicity.**
E		**. . . has no evidence of carcinogenicity for humans.**

1.6 HOW CAN [SUBSTANCE X] AFFECT CHILDREN?

Insert the following boilerplate before the child health effects discussion.

> **This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans.**

Within each topic designated by a bullet, conclusions of human studies should be discussed before those of animal studies. Topics marked by a closed bullet (●) *must* be discussed, if only to say that no information is available. Issues marked by a open bullet (○) should not be discussed if there is no relevant information.

This section, like all of chapter 1, should be written by scientists drawing on the remainder of the profile as a source of information, with assistance from risk communicators and editors in making the material accessible to the lay public. This section is not to be written with other risk communication information [such as fact sheets from other state and federal agencies] as the primary source, although the authors should be familiar with other sources of risk communication information about [Chemical X]. If the chapter 1 authors find information in other risk communication sources that they think should be included in chapter 1, but is not in any of the other chapters of the Toxicological Profile, they should discuss the matter with the principal author and authors of the appropriate chapters and the Chemical Manager to see if additional information and references need to be added to the body of the profile. **All statements made in this section are to be backed up by scientific data and references in the body of the profile.** Please collaborate closely with ATSDR in developing this section.

This section should be a summary of the issues discussed in **3.7 Children's Susceptibility** and **6.6 Exposures of Children**. Special issues concerning extrapolation from animals to humans may need to be explained. Discuss the following issues and, when necessary for clarity, define the specific stages of growth and development to which the statements apply. Exposure issues should be discussed before health effects. These issues should be discussed:

- Are children exposed or likely to be exposed to [Chemical X]? How?
- Are unique exposure pathways for children known? Examples include soil and paint pica and hand-to-mouth activity.

- Are the parents' work clothes likely to be a source of exposure to children? This topic should only be mentioned if 6.6 contains specific evidence about documented take-home exposures.

- Are parents' lifestyles or cultural practices (e.g., the use of mercury in occult practices such as Santeria, Voodoo, and Espiritismo or in folk remedies for stomach disorders in Indian and Asian populations) likely to be a source of exposure to children?

- Are [Chemical X] vapors heavier than air? If so, use the following text:

  > "[Chemical X] vapors are heavier than air and since young children are closer to the ground or floor because of their height, they may be exposed to more [Chemical X] vapors than adults during accidental exposures."

- Are significant dietary exposures likely? Remember that a child=s diet often differs substantially from that of adults.

- Are children more or less likely than adults to be exposed to [Chemical X]? In other words, are children likely to be different in their weightBadjusted intake of the toxicant?

- What health effects have been observed in children? Are there health effects observed in adults that are also of potential concern in children? What health effects have been observed in adults exposed to [Chemical X] during childhood? What conclusions about children can be drawn from animal studies? If there are no data on children, state that AThe effects of [Chemical X] have not been studied in children, but they would likely experience the same health effects seen in adults exposed to [Chemical X].

- Does the susceptibility of children to the health effects from [Chemical X] differ from that of adults? Describe how (greater, lesser) and if possible why (i.e., are pharmacokinetics and metabolism different in children?). Are data adequate to draw conclusions? What do animal studies suggest? Are there theoretical reasons why children might differ from adults in susceptibility? When appropriate use statements such as: AWe do not know whether children differ from adults in their susceptibility to health effects from [Chemical X].@ AChildren (may need to specify age) are more/less susceptible to health effects from [Chemical X] than adults.

- Is the developmental process altered by the toxicant? Developmental problems may include functional neurological development, such as learning deficits and deficits in social behavior, and may result from postnatal as well as prenatal exposure. Discuss the effects in humans and then in animals. [Note that authors should now omit discussion of developmental effects in **1.5 How Can [Chemical X] Affect My Health?**]

- Can [Chemical X] or its active metabolites reach (from inhalation, oral, or dermal exposure to the mother) and cross the placenta? Have measurements been made of [Chemical X] or its metabolite levels in amniotic fluid, meconium, cord blood, or neonatal blood that indicate prenatal exposure? The issue of background levels may need to be discussed.

Relevant intraperitoneal (i.p.) or intravenous (i.v.) data may be mentioned in context, if appropriate.

- Can [Chemical X] or its active metabolites reach (from inhalation, oral, or dermal exposure to the mother) and be excreted in breast milk? Have significant quantities been measured in breast milk? The issue of background levels may need to be discussed. Relevant intraperitoneal (i.p.) or intravenous (i.v.) data may be mentioned in context, if appropriate.

- Is [Chemical X] stored in maternal tissues *during pre-conception exposure*, and if so, can these stores be mobilized during pregnancy or lactation? Will this process result in exposure to the embryo/fetus or neonate?

- Does [Chemical X] or its metabolites indirectly affect the fetus? Examples include interference with blood flow, oxygen, or nutrient transport to the placenta or with waste transport from the placenta.

- Does [Chemical X] or its metabolites indirectly affect the neonate during lactation?

- Are pharmacokinetics known or suspected to be different in children?

- Is metabolism of [Chemical X] known or suspected to be different in children? If the enzymes that metabolize [Chemical X] are known, does their expression or activity differ in children in general?

- Is the mechanism of action known or suspected to be different in children?

- How can parental exposure affect children?

- Discuss any issues related to childhood cancer and either prenatal or postnatal exposures to [Chemical X].

- Are there any biomarkers of exposure or effect that have been validated in children or in adults exposed to [Chemical X] during childhood? Are there any biomarkers of exposure or effect unique to children?

- Are there any interactions with other chemicals that are unique to children?

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO [SUBSTANCE X]?

Risk communication messages about how parents can reduce their children=s exposures to [Chemical X] should be included in this section. Some of these methods may also reduce adult exposures. **When outlining this section, please think carefully about the sources of exposure mentioned in chapter 6 and the uses mentioned in chapter 5. Are there steps an *individual* might take to reduce exposures of their children?** Statements made in this section should be consistent with the remainder of the Toxicological Profile, in particular **6.6 Exposures of**

Children and the author should actively check for consistency during profile preparation. Consider the exposure scenarios discussed in any case studies mentioned in the Toxicological Profile that resulted in health effects in children and whether any of these exposures could have been prevented by parents. Remember that sources of exposure for the general populations are also frequent sources of exposure for children and that these sources of exposure might be potential targets for intervention. **The major focus of this section should be on minimizing or preventing realistic exposure situations for significant doses of [Chemical X] to children; however, prudent or no/low cost or low effort strategies to reduce exposures from other potential sources of [Chemical X] may also be discussed.**

Consult the ATSDR Web site (http://www.atsdr.cdc.gov/) to see if any appropriate suggestions are made in the Alerts, Health Advisories, or other posted information. Also consult the CDC Prevention Guidelines Database (http://aepo-xdv-www.epo.cdc.gov/wonder/PrevGuid/PrevGuid.htm) to see if any of these documents have relevant advice or examples. Check with the Occupational Safety and Health Administration (OSHA), the Environmental Protection Agency (EPA), the National Institute for Occupational Safety and Health (NIOSH), the National Institute of Environmental Health Sciences (NIEHS), the Consumer Product Safety Commission (CPSC), the Centers for Disease Control and Prevention (CDC), and ATSDR to see if appropriate risk communication material on relevant topics is already available and could be used as a source of ideas [see partial list of resources in **Attachment F**]. Another potential source of ideas is *Raising Children Toxic Free* by Herbert L. Needleman and Philip J. Landrigan (Farrar, Straus, and Giroux, Inc., New York, NY, 1994). **The chapter 8 author should already have checked the EPA fish and wildlife advisory database [http://www.epa.gov/OST/fishadvice/] to see if there are any recommendations based on [Chemical X] and that they have been mentioned in Table 8-1**. If any such advisories exist, they should be discussed here (see later example).

Risk communication information from sources other than ATSDR is to be used as a source of ideas, not as a source of scientific information. Copies of other risk communication information used as a *source of ideas* for writing this section should be delivered to ATSDR with the appropriate draft. This section, like all of chapter 1, should be written by scientists drawing on the remainder of the profile as a source of information, with assistance from risk communicators and editors in making the material accessible to the lay public. It is not to be written with other risk communication information [such as fact sheets from other state and federal agencies] as the primary source, although the authors should be familiar with other sources of risk communication information about [Chemical X]. **All scientific statements made in this section are to be backed up by scientific data and references in the body of the profile.**

If information that should be included in chapter 1 is found in other risk communication sources but is not discussed in the other chapters of the Toxicological Profile and should be, this situation should be communicated to the principal author and other appropriate chapter authors immediately. In many cases, there may be a valid reason for not including this particular information in chapter 1. However, the principal author and authors of the appropriate chapters should jointly consider, in consultation with ATSDR, whether relevant information is missing from the body of the Toxicological Profile, and decide whether a supplemental search or a review of the original search(s) and literature selection strategy is needed. Authors of chapters 3

and 6, and chapter 1 as appropriate, should be familiar with both the main literature search strategy and any supplemental search strategies used for [Chemical X] and whether these searches are likely to have missed any relevant resources. **Authors of chapters 1, 3, and 6 are responsible for instigating supplemental literature searches [see Literature Search] as necessary.** The need for a supplemental literature search may become obvious at any time during Toxicological Profile development.

Issues will occasionally arise in the preparation of 1.7 **How Can Families Reduce the Risk of Exposure to [Chemical X]?** About the effectiveness of certain prevention strategies and related issues that would not ordinarily be discussed in the body of the profile. Minor searches of appropriate databases may be necessary. Discuss with ATSDR whether additional information should be cited in the body of the Toxicological Profile. Be sure that regulations or recommendations about [Chemical X] from other government agencies that are discussed in this section are also discussed in **Chapter 8: Regulations and Advisories**.

Please collaborate closely with ATSDR in developing this section. **AVOID UNNECESSARILY ALARMIST STATEMENTS.**

Consider the following issuesCand any other appropriate onesCin writing this section. These suggestions are not a comprehensive list of potential issues. Within each topic designated by a bullet, conclusions of human studies should be discussed before those of animal studies. The discussion of relevant prevention strategies does not have to be in the order these issues are raised in the following list. Organize this section so that the prevention of the greatest sources of exposure is discussed first. Note that in some instances, there may be no actions an individual can take to reduce their children=s exposure, and in such cases this section will consist of boilerplate alone.

The following boilerplate text should be included:

If your doctor finds that you have been exposed to significant amounts of [Chemical X], ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

- If screening of childrenCas a public health practiceCfor exposure to [Chemical X] is appropriate, explain when. An example is blood lead screening. What have ATSDR and CDC recommended? Relevant recommendations by EPA, the World Health Organization (WHO), and other agencies may be discussed if appropriate.

- Are there nutritional deficiencies that enhance the absorption or change [for the worse] the distribution, metabolism, or excretion of [Chemical X]? [Example: influence of calcium and iron deficiencies and fasting on absorption of lead]. Suggest a balanced diet with adequate amounts of [relevant nutrient].

- Are there accurate and costBeffective methods for testing or surveying homes for [Chemical X]? When should homes be screened for the presence of [Chemical X]? Examples: radon testing, lead testing, visually inspecting for exposed asbestos.

- Are structural materials of the home (e.g., lead from plumbing and radioactivity from certain construction materials made of particular mining slags) likely to release [Chemical X]? Is testing or remedial action feasible?

- Are significant amounts of [Chemical X] likely to be in finished drinking water? Can the water content be easily tested? Are there practical remedies? If [Chemical X] is in the public drinking water supply, do any relevant federal regulations apply to the supplier?

- Are there hobbies conducted in the home that might expose children? [Lead solder used in making stained glass; solvent use, etc.?] How can exposure be minimized? [Ventilation?]

- Discuss EPA and Food and Drug Administration (FDA) recommendations about decreasing exposure, if appropriate.

- Are there regulations about the presence of [Chemical X] in schools? Provide a brief description. Example: asbestos.

- Are particular incidents (e.g., children playing with mercury) likely to be sources of exposure to children?

- Is [Chemical X] used on pets? Is there a risk of significant exposure to children? Are there alternatives?

- Are significant amounts of [Chemical X] likely to be on objects that children might place in their mouths? Explain.

  Possible text includes:

  > -You should discourage your children from putting foreign objects in their mouths. Make sure they wash their hands frequently and before eating. Discourage your children from putting their hands in their mouths or from other handBtoBmouth activity.

- Are significant amounts of [Chemical X] likely to be found in dirt in a bioavailable form? Under what circumstances? Possible text includes:

  > "Some children eat a lot of dirt. You should discourage your children from eating dirt. Make sure they wash their hands frequently and before eating. Discourage your children from putting their hands in their mouths or other handBtoBmouth activity."

- If [Chemical X] is found in common household products, is it present in a form or amount that makes acute ingestion of toxic quantities by young children a possibility? If so, use the following text:

"Household chemicals should be stored out of reach of young children to prevent accidental poisonings [or skin burns]. Always store household chemicals in their original labeled containers. Never store household chemicals in containers that children would find attractive to eat or drink from, such as old soda bottles. Keep your Poison Control Center=s number next to the phone."

- If [Chemical X] is found in common household products, are children likely to be exposed to significant amounts of [Chemical X] while the products are being used by adults? If so, are there easy precautions that can be taken to minimize exposure, such as following the package instructions about proper ventilation?

- Are older children likely to be exposed to toxicologically significant amounts of [Chemical X] by sniffing household or commercial products? Possible text:

  "Sometimes older children sniff household chemicals in an attempt to get high. Your children may be exposed to [Chemical X] by inhaling products containing it. Talk with your children about the dangers of sniffing chemicals."

- Is [Chemical X] contained in household items (e.g., dishes, miniBblinds, and broken thermometers) that might pose a risk of significant exposure to children? Is there an easy way of minimizing exposure? Is there an easy and accurate way of testing these items for the presence of [Chemical X]?

- If [Chemical X] is likely to be spilled in the home, is it hazardous to clean it up yourself? Clearly explain when it is appropriate to call the local fire department, poison control center, or local or state health department for assistance.

- Do NOT make any statements about screening breast milk for contaminants and the advisability of breast feeding without consulting ATSDR. There are significant benefits from breast feeding. ATSDR and CDC do not wish to make recommendations without carefully weighing the risks of exposure against the benefits of breast feeding.

- Is [Chemical X] in any mainstream pharmaceuticals used on children? Are there alternatives? An example is lindane (γ-hexachlorocyclohexane) being used for ridding children of head lice. [See Sanford Antimicrobial Guide for effective alternatives.] Instead of instructing parents not to use lindaneBcontaining lice treatment on their children, tell them: "You may expose your child to lindane if you use lindane to treat lice on your child's head. There are alternatives that do not involve the use of lindane."

- Identify any folk remedies or cultural practices that might result in significant exposure of children to [Chemical X]. Explain the common names of [Chemical X] and where it might be purchased. Do not order the reader not to engage in these practices, but rather tell them "If you use [common name] in a practice unique to your heritage, then you are using [Chemical X] and may expose your child." This statement may need to be modified to fit the details of a particular cultural practice and to explain exactly how it might expose children.

- If [Chemical X] is used as a medicine, folk remedy, or cosmetic, is the place where it is kept (e.g., the medicine cabinet) accessible to young children? Is it in a bioavailable form? Suggest to the reader that [Chemical X] should be kept out of children's reach to avoid accidental poisonings.

- Is take-home or secondary exposure (e.g., to lead and asbestos) from parental jobs likely to be a problem? See *Report to Congress on Workers' Home Contamination Study Conducted Under The Workers' Family Protection Act* (NIOSH 1995) for a good review of the literature and examples of chemicals likely to be taken home inadvertently. **This topic should not be discussed here unless there is actual evidence of take-home exposure discussed in chapter 6.** Some possible text:

  "It is sometimes possible to carry [Chemical X] from work on your clothing, skin, hair, tools, or other objects removed from the workplace. This is particularly likely if you work in [identify industries]. You may contaminate your car, home, or other locations outside work where children might be exposed to [Chemical X]. You should know about this possibility if you work with [Chemical X]. "

  "Your occupational health and safety officer at work can and should tell you whether chemicals you work with are dangerous and likely to be carried home on your clothes, body, or tools and whether you should be showering and changing clothes before you leave work, storing your street clothes in a separate area of the workplace, or laundering your work clothes at home separately from other clothes. Your employer should have Material Safety Data Sheets (MSDSs) for many of the chemicals used at your place of work, as required by the Occupational Safety and Health Administration (OSHA). Information on these sheets should include chemical names and hazardous ingredients, important properties (such as fire and explosion data), potential health effects, how you get the chemical(s) in your body, how to properly handle the materials, and what to do in an emergency. Your employer is legally responsible for providing a safe workplace and should freely answer your questions about hazardous chemicals. Your OSHA-approved state occupational safety and health program or OSHA can answer any further questions and help your employer identify and correct problems with hazardous substances. Your OSHA-approved state occupational safety and health program or OSHA will listen to your formal complaints about workplace health hazards and inspect your workplace when necessary. Employees have a right to seek safety and health on the job without fear of punishment."

- Are children likely to be exposed to toxicologically significant amounts of [Chemical X] in the diet?

  Consumption of animal products: Discuss the data in chapter 6. If there are FDA recommendations, guidelines, or regulations in Table 8-1, discuss these next. Then, if an advisory about fish or game consumption based on the presence of [Chemical X] is mentioned in Table 8-1, use the following text and modify as appropriate.

"You or your children may be exposed to [Chemical X] by eating certain types of fish or wildlife caught from certain locations. Certain states, Native American tribes, and U.S. territories have issued fish [and wildlifeCspecify the species: fish (freshwater or saltwater), turtles, type of ducks, frogs, moose, woodchucks, etc.] advisories to warn people about [Chemical X]Bcontaminated fish [and/or wildlife]. Each state, Native American tribe, or U.S. territory sets its own criteria for issuing fish and wildlife advisories. A fish [or wildlife] advisory will specify which bodies of water [or hunting areas] have restrictions. The advisory will tell you what types and sizes of fish [or game] are of concern. The advisory may completely ban eating fish [or game] or tell you to limit your meals of a certain fish [or game] type. For example, an advisory may tell you to eat a certain type of fish no more than once a month. The advisory may tell you only to eat certain parts of the fish [or game] and how to prepare or cook the fish [or game] to decrease your exposure to [Chemical X]. The fish [or wildlife] advisory may be stricter to protect pregnant women, nursing mothers, and young children. To reduce your children=s exposure to [Chemical X], obey fish [or wildlife] advisories. Information on Fish and Wildlife Advisories in your state is available from your state health or natural resources department. Signs might also be posted in certain fishing [and hunting] areas."

Consumption of produce: Discuss the data in chapter 6. Also see the following issues concerning pesticides.

- If [Chemical X] is a pesticide, consider the following issues:

  Is the pesticide used around the home?

  "If you buy over-the-counter pesticide products to apply yourself, be sure the products are in unopened pesticide containers that are labeled and contain an EPA registration number. Carefully follow the instructions on the label. If you plan to spray inside, make sure the pesticide is intended for indoor use."

  "If you feel sick after a pesticide has been used in your home, consult your doctor or local poison control center."

  If the pesticide is commonly used in the home or garden, are there safer and effective alternatives? Only discuss this issue if you can find reputable scientific evidence for workable alternatives.

  Is the timing of reBentry after pesticide application an exposure issue? If there are reliable data about the need for children to wait longer for reBentry than commonly suggested on labels, discuss these data. For example, there have been multiple reports about measurement of chlorpyrifos residues on children=s toys and the floor and carpet after the specified reBentry time has elapsed. Otherwise, use the following text:

> "Children can be exposed to pesticides by entering a room or playing on a lawn too soon after a pesticide has been applied. Carefully read and follow the directions on the pesticide label about how long to wait before reBentering the treated area."

Could accidental ingestion of household pesticides result in poisonings?

> "Pesticides and household chemicals should be stored out of reach of young children to prevent unintentional poisonings. Always store pesticides and household chemicals in their original labeled containers. Never store pesticides or household chemicals in containers children would find attractive to eat or drink from, such as old soda bottles."

Has [Chemical X] been banned or restricted for home, farm, or commercial use? Another series of misuse incidents, such as occurred with methyl parathion, would be regrettable. Use the following text:

> "Your children may be exposed to [Chemical X] if an unqualified person applies pesticides containing it around your home. In some cases, the improper use of pesticides banned for use in homes has turned homes into hazardous waste sites. Make sure that any person you hire is licensed and, if appropriate, certified to apply pesticides. Your state licenses each person who is qualified to apply pesticides according to EPA standards and further certifies each person who is qualified to apply Arestricted use@ pesticides. Ask to see the license and certification. Also ask for the brand name of the pesticide, a Material Safety Data Sheet (MSDS), the name of the product's active ingredient, and the EPA registration number. Ask whether EPA has designated the pesticide Afor restricted use@ and what the approved uses are. This information is important if you or your family react to the product."

> "If you buy over-the-counter pesticide products to apply yourself, be sure the products are in unopened pesticide containers that are labeled and contain an EPA registration number. Carefully follow the instructions on the label. If you plan to spray inside, make sure the pesticide is intended for indoor use."

> "If you feel sick after a pesticide has been used in your home, consult your doctor or local poison control center."

Is [Chemical X] likely to be on produce, either commercially grown or homegrown? Is [Chemical X] more likely to be on imported produce (i.e., has it been banned in the United States, but not elsewhere)?

> [Give some general information about FDA regulation of pesticide residues, their sampling methodology (random?), whether test results are likely to be available before food is distributed, and what assumptions are made in their analysis about whether the peel of various fruits and vegetables will be eaten. Explain the role

of EPA]. Clearly explain whether human health effects were considered in setting relevant regulatory levels [tolerances, etc.]. Make it clear that produce sold in the United States should generally have minimal amounts of pesticide residues.

If pesticide residues are likely to be on the surface of produce when it reaches the consumer, discuss whether there are effective methods of removing it (e.g., washing, scrubbing with water, or washing with water containing extremely diluted dishwashing liquid). Only discuss this issue if reputable scientific data can be found for the effectiveness of these methods. Should peeling be considered? Explaining that washing produce also reduces potential microbial contamination of the food surface may be appropriate.

- If there are any additional unique exposure pathways for children that are preventable (e.g., treated playground equipment), explain how parents could prevent the exposure of their children.

An extensive example of appropriate text for a section on mercury follows, as well as suggestions for issues to be discussed for lead.

Mercury:

"Children are often exposed to metallic mercury when they play with it. Metallic mercury is a heavy, shiny, silver liquid. When metallic mercury is spilled, it forms little balls or beads. Children sometimes come into contact with metallic mercury when they trespass in abandoned warehouses and closed factories. Children have taken metallic mercury from school chemistry and physics labs. Broken thermometers are another source of metallic mercury. Sometimes children find containers of metallic mercury that were improperly disposed of, or adults bring home metallic mercury from work on purpose. To protect your children from metallic mercury, tell them not to play with shiny, silver liquids. Schoolteachers (particularly science teachers) and school staff need to know about students' fascination with metallic mercury. Teachers and school staff should tell children about its dangers (that is, getting sick from touching and breathing mercury), and they should keep metallic mercury in a safe and secured area (such as a locked storage room) so that children do not have access to it without the supervision of a teacher. Metallic mercury evaporates slowly, and children can breathe toxic mercury vapors if it is not stored in a closed container."

"If you use metallic mercury in religious practices, you may expose your children or unborn child and contaminate your house. Such practices include Santeria (a Cuban-based religion whose followers worship both African deities and Catholic saints), voodoo (a HaitianBbased set of superstitions and secret rites), Palo Mayombe (a secret form of ancestor worship practiced mainly in the Caribbean), or Espiritismo (a spiritual belief system native to Puerto Rico), and other folk or magical practices. Metallic mercury is sold under the name "azogue" in stores (which are sometimes called botanicas) that specialize in religious items. Some people in Hispanic communities (such as family members,

spiritualists, card readers, and santeros) recommend azogue for religious practices. Typically, azogue is carried on one's person in a sealed pouch prepared by a spiritual leader, or it is sprinkled in the home or car. Some store owners suggest mixing azogue in bath water or perfume. Some people place azogue in devotional candles. Because metallic mercury evaporates into the air, it is a health risk to anyone spending a substantial amount of time in a room where the mercury is sprinkled or spilled onto the floor, put in candles, or kept in open containers."

"A small amount of metallic mercury (for example, a few drops) can raise air concentrations of mercury to levels that can be harmful to health. Metallic mercury and its vapors are extremely difficult to remove from clothes, furniture, carpet, floors, walls, and other items. The mercury contamination can remain for months or years. The use of metallic mercury in a home or apartment not only threatens the health of people who live there now, but also threatens future residents who do not know about the contamination."

"Metallic mercury is used in many household products and industrial items, including thermostats, fluorescent light bulbs, barometers, glass thermometers, and some blood pressure machines. You must be careful when you handle and dispose of all items that contain metallic mercury. If small amounts of mercury are spilled, be very careful while cleaning it up. Do not try to vacuum spilled metallic mercury. Using a vacuum cleaner to clean up the mercury causes the mercury to evaporate into the air, creating greater health risks. Mercury also ruins the vacuum cleaner. Metallic mercury vapors are very toxic and cannot be smelled. Try not to breathe mercury dust, vapor, mist, or gas, and try not to let metallic mercury contact your eyes, skin, or clothing. If you think you have been exposed directly to metallic mercury, wash yourself thoroughly and discard contaminated clothing by placing it in a sealed plastic bag. "

"If a thermometer breaks, remove children from the area. Clean up the beads of metallic mercury by carefully rolling them onto a sheet of paper or sucking them up with an eye dropper. After picking up the metallic mercury, put it into a plastic bag or airtight container. The paper or eye dropper should also be bagged. Both these bags should be disposed of properly according to instructions provided by your local health department or environmental officials. Try to ventilate the room with outside air, and close the room off from the rest of the home. Use fans for a minimum of 1 hour to speed the ventilation. If larger amounts of metallic mercury are found (for example, a jar of it), make sure the metallic mercury is in an airtight container, and call your local health department for instructions on how to safely dispose of it. If an open container of mercury does not have a lid, place a piece of plastic wrap around the top and wash your hands thoroughly. If a larger amount is spilled, leave the area and contact your local health department and fire department. Do not simply throw metallic mercury away, but instead seek professional help."

"If you notice that a child has metallic mercury on his or her clothing, skin, or hair, call the fire department and let them know the child needs to be decontaminated. "

"ATSDR and EPA do not recommend using uncontained metallic (liquid) mercury (that is, mercury not properly enclosed in glass as it is in thermometers) in homes, automobiles, day care centers, schools, offices, and other buildings. "

"Some Chinese and Indian folk remedies for stomach disorders (for example, herbal balls) contain mercury. If you give these herbal balls to your children, you may harm them. If you are pregnant or nursing a baby and you use mercuryBcontaining folk remedies, you could pass the mercury to your unborn child or your baby. It is wise to know the ingredients of any medicines you or your children take. If you keep mercuryBcontaining folk remedies in your home, make sure your children cannot reach the remedies, because they could be poisoned by mistake."

"You or your children could be exposed to methyl mercury by eating certain types of fish caught from certain locations [or wildlifeCstate species, if applicable after searching EPA database]. Certain states, Native American tribes, and U.S. territories have issued fish [and wildlifeCspecify the species: fresh or saltwater fish, turtles, type of ducks, frogs, moose, woodchucks, etc.] advisories to warn people not to eat fish [and/or wildlife] contaminated with methyl mercury. Each state, Native American tribe, or U.S. territory sets its own criteria for issuing fish and wildlife advisories. A fish [or wildlife] advisory will specify which bodies of water [or hunting areas] have restrictions. The advisory will tell you what types and sizes of fish [or game] are of concern. The advisory may completely ban eating fish or tell you to limit your meals of a certain fish type. For example, an advisory may tell you to eat a certain type of fish no more than once a month. The advisory may tell you only to eat certain parts of the fish [or game] or how to prepare and cook the fish [or game] to decrease your exposure to methyl mercury. The fish [or wildlife] advisory may be stricter to protect pregnant women, nursing mothers, and young children. To reduce your children's exposure to methyl mercury, obey fish [and/or wildlife] advisories. Information on Fish and Wildlife Advisories in your state is available from your state public health or natural resources department, and signs may be posted in certain fishing [and hunting] areas." [Note that this paragraph will need to be modified as appropriate after the EPA database on Fish and Wildlife Advisories is searched.]

[Discuss Food and Drug Administration (FDA) recommendations not to eat shark or swordfish more than once a week because of higher mercury levels in these predatory fish.]

Lead:
The following issues should be considered in constructing this section:

- "Parents should know whether the paint in their house contains lead. Lead was banned in household paint in 1978, but if your house or apartment was built before then, it might still have lead paint on the walls. Decaying, peeling, or flaking paint can cause household dust to become full of lead, and the paint may need to be fixed. If your paint is decaying or your child has symptoms of lead poisoning, you may want to have your house tested for lead. Lead can be measured in dust or directly in paint. Contact your state or local health department about testing. The National Lead Information Center (1-800-532-3394) has a listing of approved risk assessors (people who have met certain criteria and are qualified to

assess the potential risks at a given site) and of approved testing labs (for soil, paint, and dust)."

"Sanding surfaces painted with leadBbased paint or using heat to peel the paint may cause exposure to high levels of lead; therefore, any renovations should be done by a licensed contractor who will minimize exposures to household members from the distribution of leadBcontaining dust. It is important for the area being renovated to be isolated from the rest of the house because of leadBcontaining dust. The federal government requires that contractors who test for or remove lead must be certified by EPA or an EPABapproved state program. Ask to see the certifications of potential contractors. Your state health department or environmental protection division should be able to identify certified contractors for you. The National Lead Abatement Council (P.O. Box 535, Olney, MD 20932; telephone 301-924-5490) can also send you a list of certified contractors."

"If you are buying a home that was built before 1978, you may want to know if it contains leadBbased paint. The federal government requires that a person selling a home must tell the real estate agent or person buying the home of any known leadBbased paint hazards on the property."

- "Prevent your child from eating paint chips or chewing on the woodwork if you live in a house that has leadBbased paint. If you live in a house that has leadBbased paint, lead may be in household dust and, thus, on objects that children might place in their mouths. You should discourage your children from putting foreign objects in their mouths. Make sure they wash their hands frequently and before eating. Discourage your children from putting their hands in their mouths or other handBtoBmouth activity."

- "Discuss situations in which blood lead screening of children is appropriate. Note that the most recent CDC recommendations (*Screening Young Children for Lead Poisoning*, CDC 1997) are for targeted screening of children who are at high risk for lead poisoning and not for universal screening. Please consult this publication and briefly discuss the highBrisk situations for which parents might want to have their child tested. Describe what will happen during a blood lead test: A...your child=s finger will be thoroughly cleaned to prevent contamination of the blood sample with lead from the environment, and the finger will be pricked so that blood can be collected. If this test shows your child has blood lead concentrations greater than a certain amount, your health care provider will then draw blood from your child=s vein and test it to confirm the presence of lead. Blood drawn from a vein is less likely than blood drawn from a finger capillary to be contaminated with environmental lead during the process of drawing the blood."

- "Some children eat a lot of dirt. If dirt around your home contains lead, you should prevent your children from eating the dirt. Make sure they wash their hands frequently and before eating. Discourage your children from putting their hands in their mouths or other hand-to-mouth activity."

- "Many folk remedies (such as greta, azarcon, coral, payBlooBah, and rueda) contain lead. If you give your children these substances, you will expose them to lead. [Are all of these medicines used orally? Is the lead in a form it can be absorbed? Delete or modify previous sentence as necessary.] If you are pregnant or nursing and use leadBcontaining folk remedies, you may expose your children. [Check about adult gastrointestinal absorption of the forms of lead in these remedies and whether they can be transferred across the placenta or into breast milk; if not, then delete previous sentence.] It is wise to know the ingredients of any medicines you or your children take. If you keep leadBcontaining folk remedies in your home, make sure your children cannot reach the remedies because they could be poisoned by mistake."

- Investigate claims about lead-containing hair dyes and whether the lead is in a form that would be dangerous to children around adults who have dyed hair. Only discuss this if it is likely to be a source of a significant dose. Scientific data should be discussed in chapter 6. Is there a risk that children might swallow such dyes or dermally absorb them?

- If the lead in non-Western cosmetics (such as surma and kohl) is in a form that could be absorbed by humans, this needs to be mentioned. Is there a risk that children might swallow such cosmetics or dermally absorb them?

- Because fasting and nutritional deficits of iron and calcium enhance lead absorption (see **3.3.1 Toxicokinetics: Absorption)**, suggest that children should eat a balanced diet with adequate amounts of calcium and iron.

- Please discuss in chapter 6 whether the amount of exposure from certain hobbies would be measurable and of health significance. If scientific references confirm this situation, then the following points might be discussed in this section. State whether practicing some hobbies, such as using lead solder to make stained glass or for other purposes, cutting or sawing colored glass that may contain lead, and casting ammunition or fishing weights may get lead into the air. Discuss appropriate prevention strategies [Never doing these hobbies in a room with children? Using a room well ventilated with outdoor air? Changing clothes before entering other household areas? Air filters?] if scientific data are available.

- Discuss takeBhome or secondary exposure. In addition to information in chapter 6 of the profile, see *Report to Congress on Workers' Home Contamination Study Conducted Under The Workers' Family Protection Act* (NIOSH 1995) for a good review of the literature. Some possible text:

  > "It is sometimes possible to carry lead from work on your clothing, skin, hair, tools, or other objects removed from the workplace. This is particularly likely if you work in [identify industries]. You might contaminate your car, home, or other locations outside work where children could then be exposed to lead. You should know about this possibility if you work with lead."
  >
  > "Your occupational health and safety officer at work can and should tell you whether chemicals you work with are dangerous and likely to be carried home on your clothes,

body, or tools and whether you should be showering and changing clothes before you leave work, storing your street clothes in a separate area of the workplace, or laundering your work clothes at home separately from other clothes. Your employer should have Material Safety Data Sheets (MSDSs) for many of the chemicals used at your place of work, as required by the Occupational Safety and Health Administration (OSHA). Information on these sheets should include chemical names and hazardous ingredients, important properties (such as fire and explosion data), potential health effects, how the chemical gets in your body, how to properly handle the materials, and what to do in an emergency. Your employer is legally responsible for providing a safe workplace and should freely answer your questions about hazardous chemicals. Your OSHABapproved state occupational safety and health program or OSHA can answer any other questions and help your employer identify and correct problems with hazardous substances. Your OSHABapproved state occupational safety and health program or OSHA will listen to your formal complaints about workplace health hazards and inspect your workplace when necessary. Employees have a right to seek safety and health on the job without fear of punishment."

- "Lead is sometimes found in pottery and ceramics, where it is used in the glaze. In 1990, FDA issued recalls and warnings about leachable lead in pottery. In 1991, FDA set limits on the leachable lead in pottery and ceramics. To limit your child's exposure to lead from this source, do not use earthenware for storing acidic food, be careful of products purchased in other countries, do not use antiques or lead crystal to hold food or drinks, and be careful of ceramics made by hobbyists.@ Discuss the lead-testing kits that are widely available in stores. Are they an accurate method of determining ceramic/pottery lead content?" You will need references in chapter 6 documenting all the points mentioned in this paragraph.

- "Ink containing lead is often used to print labels on bread bags and other food wrappers. If you reuse bread bags for storing food, make sure they are used right side out so that the printing does not touch the food." You will need to supply references documenting these facts in chapter 6.

- Is lead in drinking water a significant enough exposure pathway to worry about? Some possible text follows, but you will need to document these facts by discussing published exposure studies on this topic in chapter 6.

  "Children may also be exposed to lead in drinking water. Some older water mains are made of lead. [Discuss legal obligations of water utility with regard to lead content of water.] Inside plumbing installed before 1930 is the most likely to contain lead. Copper pipes have replaced lead pipes in most residential plumbing. However, the use of lead solder with copper pipes is widespread. This lead solder is the major cause of lead contamination of household water in the United States. EPA recommends that anytime water in a particular faucet has not been used for 6 hours or longer, you should flush your cold water pipes by running the water until it becomes as cold as it will get (5 seconds to 2 minutes). Because lead dissolves more easily in hot water, you should use only cold water for drinking, cooking, and preparing baby formula. You may also want to have your water tested by a competent laboratory. Contact your

water supplier or local health department to get information about laboratories. [Please actually talk to a scientist in an appropriate office at EPA to see if EPA still recommends running your tap water for an interval to get out the lead that has diffused into the water while it sat overnight in the pipes. Has EPA changed its advice because of concerns about water conservation? Note that some items on the EPA web site are very old, so you do need to confirm current EPA advice.] If your water tests indicate the presence of a significant amount of lead, consult your water supplier or local health department about possible remedies. The solution may depend on the source of the lead and whether it is organic or inorganic, or particulate or dissolved."

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO [SUBSTANCE X]?

This should be a brief paragraph. The information should be consistent with that presented in Sections 3.6.2, 3.9.2, and 7.3.1. The paragraph should state whether there is a medical test or not. What can be measured? Is the test specific? Is it diagnostic of exposure and/or effect? Differentiate between substance-specific and nonspecific tests. Does the test correlate quantitatively with exposure? Can the test be used to predict potential health effects or adverse changes following exposure? How long after exposure is discontinued will the test be useful? Is the test available through most doctors' offices, or is it quite elaborate or not routinely available or used? Refer the reader to Chapters 3 and 7 for more information.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

Insert the following boilerplate at the beginning of Section 1.9.

The federal government develops regulations and recommendations to protect public health. Regulations <u>can</u> be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but <u>cannot</u> be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and

Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for [substance x] include the following:

Provide quantitative narrative on guidelines and standards for inhalation, drinking water, food, dermal exposure, etc. Accurately define and state the conditions of exposure for which the recommendations and regulations apply, e.g., 8-hour workday or 40-hour workweek. (See Eighth Set Toxicological Profile for Carbon Disulfide for a good example of how to present information in this section.) EPA Ambient Water Quality Criteria (AWQC) for fish and aquatic organisms should be included, where available, for compounds that are extremely lipophilic and have relatively high bioconcentration factors (BCFs). Differentiate between recommendations and regulations. Non-occupational health information should precede occupational health information. For occupational recommendations, do not report a short-term exposure limit (STEL) unless it is the only one listed.

Consider:

Air:	EPA, OSHA, and NIOSH
Water:	EPA Primary and Secondary Drinking Water Standards, Health Advisories, AWQC
Food:	FDA, EPA
Other:	EPA and other federal agencies, other organizations

Refer readers to Chapter 8 for further information.

1.10 WHERE CAN I GET MORE INFORMATION?

Include the following boilerplate.

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE, Mailstop F-32
Atlanta, GA 30333
Web site: www.atsdr.cdc.gov

*** Information line and technical assistance**

Phone: 1-800-CDC-INFO (1-800-232-4636) [use current phone #'s]
Fax: (770) 488-4178 [use current phone #'s]

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

*** To order toxicological profiles, contact:**

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 605-6000

CHAPTER 2. RELEVANCE TO PUBLIC HEALTH

The purpose of Chapter 2 - Relevance to Public Health is to provide to the reader an executive summary-type overview of the nature, manufacture, uses, general population exposures, and health effects of the substance under review. When confronted with making a real-time

determination of whether the presence of a particular substance in the environment poses a potential threat to human health, a public health professional should be able to obtain from this chapter sufficient information about the profiled substance to make an initial determination of whether further evaluation of the exposure scenario is warranted and of the type of health effects that primary care providers should be aware if exposure is determined to be of biological significance.

This chapter should be limited to information presented in the other chapters of the toxicological profile. The presentation in this chapter should be sufficient to provide a public health official with information that would be germane to making an initial assessment of a particular environmental scenario, but should not contain a level of detail that goes beyond this purpose. For a more detailed discussion, the reader can refer to the other chapters of the profile.

Chapter 2 should be concise (10-15 pages depending on the substance being profiled), yet informative. Statements should include references during the development stage but they should be deleted from the camera-ready final. This chapter should be separated into three sections:

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO [CHEMICAL X] IN THE UNITED STATES.
2.2 SUMMARY OF HEALTH EFFECTS
2.3 MINIMAL RISK LEVELS

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO [CHEMICAL X] IN THE UNITED STATES.

Chapter 2 should begin with a brief identification of the substance. For substances that are essential elements or nutrients, information to this effect should be included up front in the overview. A brief discussion of the basis for essentiality should be provided including the recommended dietary allowance and normal reference laboratory values.

-Chemical identification and uses? If banned, or no longer produced, say so and give some specifics dates.

> "*DDT is an organochlorine insecticide that has found a broad range of agricultural and nonagricultural applications in the United States and worldwide beginning in 1939. In 1972, DDT use was banned in the United States and in many parts of the world, except for use in controlling emergency public health problems. DDT is still used in certain parts of the world to control vector-borne diseases, such as malaria.***"**

-How is the general public likely to be exposed, what are the likely sources of exposure and important pathways for humans. Include ambient air and drinking water levels. If available, provide dietary intakes. Utilize data from large-scale studies or surveys (e.g. EPA Office of Drinking Water, FDA market basket studies, etc). Avoid data from individual studies; if this is the only information that is available, it is appropriate to include a range of values.

> *"The estimated dietary intake of PCBs for an average adult was about 0.03 ug/kg/day in 1979, but this had declined to <0.001 ug/kg/day by 1991."*

-What common lab tests (eg. blood, urine) are available to determine whether exposure occurred? (ie. biomarkers of exposure). Include normal baseline values, if available.

> *"The mean total mercury levels in whole blood and urine of the general population are approximately 1-8 μg/L and 4-5 μg/L, respectively. Recently, the International Commission on Occupational Health (ICOH) and the International Union of Pure and Applied Chemistry (IUPAC) Commission on Toxicology determined that a mean value of 2 μg/L was the background blood level of mercury in persons who do not eat fish. These blood and urine levels are "background" in the sense that they represent the average levels in blood in the general population and are not associated with a particular source for mercury. However, the intra- and interindividual differences in these biomarkers are substantial, possibly due to dental amalgams (urine) and*

ingestion of contaminated fish (blood). Long-term consumption of fish is the source of nearly all of the methylmercury measured in the general population, and individuals in communities with high fish consumption rates have been shown to have blood levels of 200 μg/L, with daily intake of 200 μg mercury."

If available, provide specific insights about the substance being discussed. For example, chapter 2 for a substance such as lead should include its use as a gasoline additive and resulting dispersal throughout the environment; its use in solder and impact to canned foods and water pipes; folk remedies; lead-based paint, etc. Such a historical perspective would be informative to the reader but also indicate any present day impacts (e.g. although many of these uses are banned, leaded paint is still prevalent in older housing and of special concern for young children who exhibit hand to mouth behavior. As lead based paint deteriorates, it contributes to indoor lead dust which accumulates floors where children crawl; lead solder may still be of concern in older housing as well).

2.2 SUMMARY OF HEALTH EFFECTS

The introduction to Chapter 2.2 - Summary of Health Effects should only include a summary of the ***most notable*** effects of the substance as will be presented in the latter part of the system/target organ section. Emphasize the human data; indicate in a general way if the animal data is supportive.

-are there any delayed effects from exposure?

-are there any long term effects from exposure?

"The preponderance of the biomedical data from human and laboratory mammal studies provide strong evidence of the toxic potential of exposure to PCBs. Information on health effects of PCBs is available from studies of people exposed in the workplace, by consumption of contaminated rice oil in Japan (the Yusho incident) and Taiwan (the Yu-Cheng incident), by consumption of contaminated fish, and via general environmental exposures, as well as food products of animal origin. As summarized below and detailed in Chapter 3, effects that have been associated with

exposure to PCBs in humans and/or animals include liver, thyroid, dermal and ocular changes, immunological alterations, neurodevelopmental changes, reduced birth weight, reproductive toxicity, and cancer. The human studies of the Yusho and Yu-Cheng incidents, contaminated fish consumption, and general populations are complicated by the mixture nature of PCBs and possible interactions between the components (see Chapter 3 for additional information). Therefore, although PCBs may have contributed to adverse health effects in these human populations, it cannot be determined with certainty which congeners may have caused the effects. Animal studies have shown that PCBs induce effects in monkeys at lower doses than in other species, and that dermal/ocular, immunological, and neurobehavioral changes are particularly sensitive indicators of toxicity in monkeys exposed either as adults, or during pre- or postnatal periods."

The non-numbered subsections of **ONLY** the **MAJOR** system/target organs section should follow immediately after the general introduction to provide a more detail.

Reproductive Effects. The subtitle is in bold and the discussion begins on the same line. The discussion should not contain references or specific experimental design information, but it should be a general discussion of scientific findings based on the weight of evidence of studies.

2.3 Minimal Risk Levels

Unlike sections 2.1 and 2.2, the discussion of minimal risk levels should contain more detail regarding citations, doses, and other relevant information. The reader should be referred to Exhibit 14 (MRL Worksheets) for more detail.

Any expert panel meetings convened for the purpose of discussing a particular profiled chemical/substance and the results of, or recommendations from, that meeting and their relevance to the MRL in particular and public health in general shall also be briefly discussed in Section 2.3. Similarly, any other factors relevant to MRL derivation which warrant specific discussion or explanation should also be presented in such a paragraph.

Inhalation MRLs

- An MRL of ___ has been derived for (duration) inhalation exposure (14 days or less) to [substance x].

Oral MRLs

- An MRL of ___ has been derived for (duration) oral exposure to [substance x].

Directly under each heading (inhalation and oral) should be the bulleted statements (shown in examples above) for the corresponding MRLs (order: acute, intermediate, and chronic). Under each bullet, discuss the key study, effect level, and target organ of effect for which the MRL was derived, and provide a brief description of studies that support the derivation or that provide evidence for the sensitivity of the endpoint selected.

When MRLs have not been derived for a specific duration, the bullets of MRLs that do not exist should be deleted. If MRLs have not been derived for a specific exposure route or duration within the route, provide a concise and accurate justification for the lack of MRLs. This information should be entered as paragraphs, not bullets. The explanation must be as clear as possible; communication between the author, chemical manager, and MRL workgroup is essential.

CHAPTER 3. HEALTH EFFECTS

OVERVIEW

Chapter 3 summarizes information regarding the health effects of the substance. The information is intended to be useful to community-level public health officials, physicians, toxicologists, and concerned citizens. ***Therefore, in all sections, emphasis must be placed on providing a synthesis and evaluation of the information available for each subsection, rather than a detailed description of the studies***. Scientifically prudent judgments, interpretations, and reasoned speculations are both appropriate and desirable. Definition of more difficult concepts, medical terms, or medical conditions should be provided in the text. In general, ATSDR prefers to avoid the use of nonstandard acronyms (those not in Exhibit 25, which appears as Appendix C in the toxicological profile). In cases where the text would flow better, certain terms that occur routinely in Section 3.2 can be substituted with scientifically acceptable acronyms, which should then be added to Appendix C of the toxicological profile. The acronym should be defined the first time it is used.

Chapter 3 is divided into subsections, as follows.

3.1 INTRODUCTION
3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE
3.3 GENOTOXICITY
3.4 TOXICOKINETICS
3.5 MECHANISMS OF ACTION
3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS
3.7 CHILDREN'S SUSCEPTIBILITY
3.8 BIOMARKERS OF EXPOSURE AND EFFECT
3.9 INTERACTIONS WITH OTHER SUBSTANCES
3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE
3.11 METHODS FOR REDUCING TOXIC EFFECTS
3.12 ADEQUACY OF THE DATABASE

A detailed description of the appropriate content of each section is provided below.

3.1 INTRODUCTION

This section begins with the following boilerplate.

> **The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of [substance x]. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.**
>
> **A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.**

If additional introductory material is necessary (e.g., to clarify the topic of discussion if the official title of the profile is potentially confusing), a brief discussion should be added. *Note: The decision as to what should be included in the text versus in the official title of the profile is the responsibility of ATSDR.* For profiles that only discuss some of the topics mentioned in the title (e.g., when the title covers more than one substance or form of a substance (such as isomers, mixtures, and compounds), clearly identify which forms will be discussed and why. This should also be mentioned in Section 1.1 (What Is [Substance X]?). The introduction to this section should also:

- Differentiate between forms of the substance or compounds discussed in the text.
- Define any acronyms or abbreviations that will be used to represent the substance(s) or compound(s).
- Discuss any important information that the reader should consider in the overall evaluation of the database.
- Provide a brief discussion of essentiality, if relevant. If the profile covers different forms or compounds, the order in which these are discussed should be constant throughout the profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

This section begins with the following boilerplate.

> **To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).**

The boilerplate continues as follows. Modify this information for profiles without LSE tables and figures and for profiles covering radionuclides.

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals or exposure levels below which no adverse effects have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

- Make the following modifications to the next boilerplate paragraph as applicable.
- Delete the paragraph if there are no cancer studies.

- Remove the EPA unit risk information if there is no unit risk available.

- Where cancer effect levels (CELs) are provided in all tables, do not provide specific table and figure numbers.

- Where CELs are not provided in all the tables and figures, include the tables and figures where they are provided. If all of these figures also have EPA unit risks, then do not include the figure numbers again under unit risk.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of [substance x] are indicated in Table(s) (provide specific table numbers) and Figure(s) (provide specific figure numbers). Because cancer effects could occur at lower exposure levels, (the) figure(s) (provide specific figure number if only one range

is given) also show(s) a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Add the following boilerplate unless no MRLs were derived.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for [substance x]. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (non-carcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on non-cancer health effects only and do not reflect a consideration of carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or result from repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

The following boilerplate should appear in all profiles:

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

For profiles that include more than one form of a substance or compound in the text, but only certain forms are entered in the LSE table or figures, a statement explaining the reason for this should be provided after the boilerplate (see Set 9). If the decision affected the entire Chapter 3, the discussion should go under the boilerplate in Section 3.1, and only the information that pertains to Section 3.2 should be entered here. If the substance was administered in different formulations (e.g., cis and trans mixtures) and quite a few different formulations were used, consideration should be given to adding a table of formulations and their composition to the introduction.

General Guidance for Section 3.2

The purpose of Section 3.2 is to specify the health effects associated with the substance and the degree of certainty attached to that association. Reliable studies showing no effect or negative data for a specific end point in which positive data exist should also be discussed. Where the database is limited, studies that are not in the tables and figures should be presented and the

limitations addressed. In cases where limitations exist, but the studies are still considered reliable enough to include in the tables and figures, a brief explanation of the limitations should be provided.

Emphasis must be placed on providing a synthesis and evaluation of the weight of evidence available on each topic, rather than a detailed description of the studies in the LSE tables. Scientifically prudent judgments, interpretations, and reasoned speculations are both appropriate and desirable. The text should consist of conclusions and supporting data to determine whether the effect occurs or not, and whether the data are reliable. Focus should be first on conclusions about occurrence in humans followed by results observed in other species. Compare and contrast effects observed in humans with those observed in laboratory animals (e.g., "These effects are consistent with the observed renal toxicity of [substance x] in humans"). If data permit, discuss the differences in exposure levels that produced effects in humans and animals (i.e., whether the levels of effect are similar or whether there are large differences in susceptibility to adverse effects). Do not discuss extrapolation of animal studies to humans in this section; the appropriate place is Chapter 2 (Relevance to Public Health). Compare health effects and effect levels for different species and strains, if relevant. This, along with the toxicokinetic data in Section 3.3, should provide the basis for discussion of relevant species in Chapter 2 and data needs in Section 3.10.

When information suggests that an effect occurs but the dose-response relationship is unclear, discuss this issue in the text. For example, if there are two well-conducted studies, one which reports renal tubular necrosis at 25 ppm and 250 ppm chronic exposure, and another which reports no effect at 50 ppm and 100 ppm but records renal necrosis at 500 ppm chronic exposure, present that information in the text. Repeating every NOAEL for sections in which there are a lot of data is unnecessary. The lowest levels of effect within a duration and end point should be provided. Differences in effects (type and level of occurrence) should be emphasized. Differences between species, strains, and gender in the response to the substance should be discussed if there is relevant variation. Consider physiological differences for humans, animals, and strains when assessing effects. This is especially important in discussing strains used for cancer studies. The exposure regimen (e.g., hour/day or days/week) need not be given for every effect in the LSE tables and figures. However, terms such as "intermittent" and "continuous" for inhalation and oral (water, food) should be used when describing the type of exposure. For oral studies, discuss differences in effects observed that might or can be attributed to the method of administration (food, capsule, water, gavage, bolus versus continuous) and vehicle used. The discussion of studies and levels in which effects occurred should flow smoothly (i.e., information should be used in context to support the conclusion). Feasible or well-accepted explanations of, or reasons for, differences in toxicity that are provided by the authors of the studies should be presented and the appropriate references cited. Use introductory statements to provide a summary of the information under each heading or a summary paragraph to provide conclusions on human and animal data (see Ninth Set Profile for Benzene for an example).

Important: Refer to General Guidance (Quality Criteria for Animal and Human Studies) and Appendices C and D of this guidance when writing this section.

Text Organization

As noted in the introductory boilerplate for Section 3.2, toxicity information should be organized according to route of exposure. Most of the information describing reliable studies should be included in the tables. Text should be reserved for conclusions, discussions, and explanations. The following major headings should be used.

3.2.1 Inhalation Exposure
3.2.2 Oral Exposure
3.2.3 Dermal Exposure
3.2.4 Other Routes of Exposure

Other routes of exposure (e.g., intraperitoneal, intramuscular, subcutaneous) and *in vitro* studies should be discussed in section 3.2.4. If no information exists, use the following boilerplate:

No studies were located regarding other routes of exposure to [substance x].

Unlike sections for inhalation (3.2.1), oral (3.2.2), and dermal (3.2.3), the information in section 3.2.4 Other Routes of Exposure should not contain headings. Only provide information on health effects that augments the information presented in the sections for inhalation, oral, and dermal exposures or that increases the understanding regarding pathogenesis of effects, mechanisms of toxicity, etc.

Studies where more than one route exist (e.g., epidemiological studies) are discussed under the principal route of exposure and cross referenced with other probable routes of exposure. Consider what is known about the toxicokinetics of the compound when deciding where to place this information.
If numerous studies suggest or establish a causal relationship but little information is available to indicate a specific route or level of exposure, the organizational scheme can be modified to present health effects in humans (exposure route unspecified) first. Where data on route are limited for humans but blood levels or other forms of quantitative exposure information exist, rearranging the organizational scheme will be necessary. The principal author should discuss all proposed changes in format or anticipated problems with the categories with the contract editor, chemical manager, and project officer. In all cases, the arrangement should attempt to provide as much information as possible on effects in humans before discussing effects in animals.

For profiles covering elements and their compounds, effect levels in the text, tables, and figures should be expressed in terms of the element. For example, text should read, "Rats received 3.18 mg silver/kg/day as silver nitrate" rather than "Rats received 5 mg/kg/day of silver nitrate."

Within each route of exposure, discussions should be presented according to effect, in the following order.

3.2.1.1 Death

3.2.1.2 Systemic Effects
- Respiratory Effects
- Cardiovascular Effects
- Gastrointestinal Effects
- Hematological Effects
- Musculoskeletal Effects
- Hepatic Effects
- Renal Effects
- Endocrine Effects
- Dermal Effects
- Ocular Effects
- Body Weight Effects
- Metabolic Effects
- Other Systemic Effects (optional)

3.2.1.3 Immunological and Lymphoreticular Effects
3.2.1.4 Neurological Effects
3.2.1.5 Reproductive Effects
3.2.1.6 Developmental Effects
3.2.1.7 Cancer

Place each effect in one or several of the categories listed above. The unnumbered heading "Other Systemic Effects" may be used to address effects not listed. If there is no data, do not include it.

These categories have been chosen so that the figures and tables can be standardized. The term "other" should be used in the tables and figures of Chapter 3 to refer only to "Other Systemic Effects," as defined above. Where effects fall under more than one category, choose the most appropriate category in which to discuss the effects and cross reference the discussion in the other categories. For example, dermal sensitization could be considered both an immunological effect and a dermal effect. Dermal sensitization should be addressed as a dermal effect and cross referenced to the immunological effects. Sensitization reactions and the mechanism of the allergic response should then be further discussed. If the chemical manager and principal author feel that doing so provides a better picture of the toxic potential of the profiled substance, the same effect can appear under more than one system category in the LSE tables and figures. However, developmental studies where exposures occurred under prenatal (only) or prenatal and

postnatal conditions should include effects to the developing organism or offspring under "developmental" in the table and not under specific effect categories, such as neurological.

Dermal and ocular effects are addressed separately, and body weight changes, endocrine effects, and metabolic effects have their own categories. Immunological effects include lymphoreticular effects, and reproductive effects are presented before developmental effects.

If equivocal data exist for any of the unnumbered headings, this fact should be stated.

All numbered headings must appear, in order, even if there are no data. Use the following boilerplate when no data are located for major headings under health effects (e.g., death, systemic effects, immunological effects).

> **No studies were located regarding [health effect] in [humans and/or animals] after [inhalation, oral, dermal] exposure to [substance x].**

When no human or animal data are located for three or more major (numbered) headings in a row, they may be collapsed in order.

No studies were located regarding the following [health effects] in [human or animals] after [inhalation, oral, and dermal] exposure to [substance x]:

3.2.2.1 Death
3.2.2.2 Systemic Effects
3.2.2.3 Immunological and Lymphoreticular Effects
3.2.2.4 Neurological Effects

When no data are located for systemic (unnumbered) headings, these headings may be collapsed in the order listed below. The boilerplate sentence should be inserted at the beginning of the systemic section and the unnumbered headings should be deleted.

No studies were located regarding cardiovascular, musculoskeletal, hepatic, renal, or dermal/ocular effects in humans or animals after inhalation exposure to [substance x].

Within each effect, discussions should be organized by species (humans first, then animals); within this breakdown, discussions should be organized by duration (acute, intermediate, chronic). Information from human and animal studies should be presented in separate paragraphs. Interpretive sentences, where possible, should be used to compare effects. If the profile covers different forms or compounds in the health effect section, there should be consistency in the order of presentation of the information. The organization should consider the degree of information available for each form or compound, the categories in which the compounds are grouped (e.g., inorganic versus organic, cis versus trans, trivalent versus hexavalent), differences in toxicity, and the relationship of the substances discussed (e.g., metabolites). The organization should be carefully planned to present the least confusion to the reader.

LSE Tables and Figures

Examples of LSE tables and figures are shown in exhibits 10, 11, and 12. A User's Guide for these tables and figures (see Exhibit 13) should be included as Appendix B of the profile. (See guidance for profile appendices for further information about the User's Guide.)

For profiles that include elements and compounds (e.g., a metal and its salts), the tables should be titled "Levels of Significant Exposure to [Substance X]," and not "Levels of Significant Exposure to [Substance X] and Compounds," because the exposure levels in the table are for the metal.

For profiles discussing more than one substance, the principal author must discuss the organization of text, tables, and figures with the contract editor, chemical manager, and project officer prior to completion of the first draft and the consistency review. The organizational scheme should allow for a clear and concise presentation of data. The amount of information available, differences in toxicity, and mode of action should be considered in the arrangement and presentation of information.

The purpose of the LSE tables and figures is to show the following:

- The effects that are seen as exposure levels increase.
- The effects that are seen as exposure duration increases.
- Differences in response by species, strain, and sex.
- Levels of exposure to humans below which the risk of adverse effects is presumed to be minimal (MRLs) for effects other than cancer.
- CELs, where data permit.
- Effects that occur at concentrations less than those that result in 100% mortality.

LSE tables and figures are computer-generated based on the supplemental document. A table should be generated for inhalation, oral, or dermal data and a figure should be created for inhalation and oral data, even if limited data points exist. These tables and figures should be presented in landscape format, with the table typeface matching other tables in the profile.

The tables and figures should be organized by effect, in the same order as described for Section 3.2 of the text. As in the text, the term "other" can be used in LSE tables and figures but should refer only to "Other Systemic Effects" and should always appear (in the table) at the end of the list of systemic effects. The term "other" must be defined in the text in parentheses after the LOAEL. There are no NOAELs for Aother@ systemic effects. In the absence of related endpoints, decreased food and water intake can be included under Aother@ systemic effects.

To facilitate clarity in presenting toxicologic data, please try to adhere to the following guidelines.

- When studies were conducted using various forms of the compound (e.g., salts, isomers, isotopes), the form used, if different from the column heading, should be indicated in the reference column under the reference. The table headings should indicate that doses (or exposures) were in mg [substance]/kg/day or mg

[substance]/m^3 (see Exhibit 11). In addition, chemical forms should be indicated in the figure with an appropriate symbol or abbreviation.

- Provide all concentration and dose calculations in the supplemental document (see guidance for the supplemental document). These will appear in the LSE table but not in the LSE figure.

- Use the term "once" instead of "1 x/day" if the substance was only administered once (e.g., one-day gavage LD_{50} studies). For inhalation studies and dermal studies conducted for less than one day, use the actual time, e.g., 4 hr, 10 min.

- The oral LSE table should indicate the dosing method using appropriate abbreviations (e.g., (F) feed, (W) drinking water, (G) gavage, (C) capsule, etc.). Indicate the vehicle used for gavage dosing (e.g., '(GW) for water, (GO) for oil, (G) for not specified. If the "neat" compound is used, discuss in the comment field.

- Separate Gd and 7-15 with a space, as Gd 7B15. This should be done for all specified durations (e.g., Ld 14B18, ppd 28B41, 2 x/day).

- The age of the animal should be specified in the "Exposure duration/frequency" category if the animal was exposed at times other than adulthood.

Examples:
5-10 d
Ld 14-18 ppd 28-41,

where Ld = lactation day(s), ppd = post-parturition day(s).

- If pulse studies are used, describe the regimen under the "Exposure Duration/Frequency" category and explain it fully under the description of study.

- Be consistent in the order in which entering information in the "Exposure Duration/Frequency" category, e.g., total number of days, number of doses per day (1 x/day, ad libitum, etc.), and condition in which exposure occurred (Gd 1-16, ppd 28-41).

- For developmental studies where exposures occurred under prenatal only or under prenatal and postnatal conditions, effects to the developing organism or offspring must be discussed under "developmental" in the table and not under specific effect categories, e.g., neurological.

Parenthetical text in the effect column should be descriptive enough to delineate between less serious and serious LOAELs. When presenting a health effect that occurs with varying severity,

the text should clearly describe the degree or magnitude of the effect (e.g., hepatic, less serious LOAEL of "small, infrequent foci of necrosis with no biochemical or functional alterations"; hepatic, serious LOAEL of "frequent focal and coalescing areas of necrosis with markedly elevated SGPT and SGOT"). Include all adverse effects noted under the end point. If the study shows both less serious and serious effects at the same dose level for the endpoints, put all the effects under the serious category.

- Clearly define the endpoint effect(s), and do not use "generic descriptions." Avoid nonspecific terms such as degeneration, severe signs of neurotoxicity, necrosis, neurological effects, CNS effects, fatty changes, and the like. For example, rather than "increased enzyme activity," specify "increased levels of SGOT, SGPT . . . ."

- The classification of endpoints should agree with the guidance. There should be consistency with respect to calling certain end points less serious and serious (see Tables 3-1— 3-17).

- For developmental studies, including those conducted during lactation, indicate if the effects were to the dam or fetus if it is not intuitively obvious (e.g., delayed vaginal opening in pups, increased heme synthesis in dams).

- If available, include percentages or ratios for effects that may occur with varying incidence or magnitude (e.g., percent resorption, percent decrease in body weight/body weight gain and number of deaths/number of test animals).

Presentation of Levels (Units, Dose)

Within the inhalation and oral sections of the profile, data on NOAELs and LOAELs are summarized in LSE tables and figures. Within the dermal section, data on NOAELs and LOAELs are summarized in an LSE table only; no LSE figure should be prepared for dermal data. All levels should be expressed as concentrations (air), administered dose (oral), or applied dose (dermal). Do not attempt to estimate absorbed dose. Where absorbed dose or dose to specific organs is estimated by the author of the study, it may be appropriate to include this in the text of the profile. If conversion from concentration in food or drinking water to estimated daily dose is required, and the necessary information (e.g., body weight, food or water consumption) cannot be obtained from the reference, refer to the following document for standard assumptions: EPA. 1988. Reference values for risk assessment. Prepared for the Office of Solid Waste, Washington, DC. Cincinnati, OH: Environmental Criteria and Assessment Office. ECAO-CIN-477.

Use mg/m^3 or ppm for inhalation as appropriate (ppm for gases, mg/m^3 for particulates) and mg/kg/day for ingestion. (If necessary use µg, ng, or another unit, instead of mg to keep dose information in the whole-number range.) For profiles covering compounds, all salts should be converted to the parent substance, and the information should be expressed in the table as units of parent compound (e.g., mg Cr/m^3 and mg Cr/kg/day, for chromium). Refer to guidance on MRLs and the supplemental document for information on conversions. For the oral and inhalation routes, the units should be the same as that specified in the column heading. An exception may be made for dermal exposure. The data for dermal exposure are often in different units and often conversions are often not possible or useful (i.e., either by using information presented in the reference or by standard conversions). For dermal exposure records, remove the units in the column heading and enter the units for each level in the table beside the level. ***All calculations and conversions must be double checked. This should be done during preparation and quality control of the supplemental document.***

What To Include in the LSE Tables and Figures

- Studies that lack quantitative estimates of NOAELs or LOAELs, or that are not reliable, should not be included in LSE tables and figures. ***Important: Refer to General Guidance (Quality Criteria for Animal and Human Studies) and Appendices C and D of this guidance when writing this section.*** All data in the inhalation and oral LSE tables must be plotted on the corresponding LSE figures. Dermal, which do not have an accompanying LSE figure.

- Do not define NOAELs for death. For studies in which death occurred, provide the number of animals that died (e.g., number of deaths/number of test animals).

- For data-poor substances, plot all reliable NOAELs, LOAELs, and CELs that are available for the substance. For data-rich substances, identify NOAELs and LOAELs for each specific effect, species, and duration (and, where applicable, each compound) from the available studies that satisfy the criteria in Attachment C (Evaluating the Quality of a Toxicological Study). After selecting the studies to be used in the LSE tables and figures, plot only the highest NOAEL values and all LOAEL values for each specific effect, species, duration, and compound *for each study*.

- Within each duration category (acute, intermediate, chronic), when duration is the only variable between two or more studies, include the study with the shortest duration for an observed effect.

Example: A

INTERMEDIATE EXPOSURE

Exposure	Frequency		Effect Level	Effect
A) Rat	50 mg/kg/d wk	14	LOAEL	Tubular necrosis
B) Rat	50 mg/kg/d wk	15	LOAEL	Tubular necrosis

In the above example, use study A.

Including Sex Differences in Exposure Levels and/or Effects in LSE Tables and Figures

There are four conditions in which sex differences must be indicated in the tables.

- Where males and females were exposed or dosed at the same or different levels and definite differences were observed between the sexes with regard to effects and/or level of effect. (See Example A that follows).

- Where different doses (accounting for differences greater than 10%) were used for males and females. For example, for male rats dosed at 50, 180, and 320 mg/kg and for female rats dosed at 30, 125, and 280 mg/kg, results should be reported as shown in Example B.

- Where only one sex was examined, the sex should be entered after each level in the table, e.g., 0.1 M (increased RBC, WBC).

- Where both sexes exhibited only NOAELs for a certain end point, only the sex showing the highest NOAEL is indicated (See Example C).

Example A. Where the sexes showed different effects at different levels, the effects and levels are entered as follows.

	NOAEL	LOAEL	LOAEL (serious)
Neurological	180 M	320 M (excitability)	30 F (convulsions)

Example B. Where both sexes showed similar effects but at different levels, the effect and levels are entered as follows.

	NOAEL	LOAEL
Respiratory	50 M	180 M (alveolar hyperplasia and increased lung weight)
	125 F	280 F

Example C. Where both sexes exhibited only NOAELs for a certain endpoint, only the sex showing the highest NOAEL is indicated.

	NOAEL	LOAEL
Renal	320 M	

In all cases, the sex of the animal should be entered one space to the right of the level, using "M" to indicate male and "F" to indicate female. (See Examples A, B, and C above.)

- When entering this information in an LSE figure, choose the most sensitive gender (i.e., the one with the lowest LOAEL) and enter this LOAEL and the corresponding NOAEL for the same sex. In Example B above, the following levels for the male should be entered: NOAEL of 50 and LOAEL of 180. In Example A above, only the serious LOAEL for the female should be entered. The gender of the animal is not specified in the LSE figure.

Where sex differences are indicated in an LSE table but not in the corresponding LSE figure, use the following boilerplate (or a modification thereof) as footnote b (after footnote a which states "The number corresponds to entries in Figure 3–___). **Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 3–___. Where such differences exist, only the levels of effect for the most sensitive gender are presented.**

Including the Strain in the LSE Table

The strain of the species should be noted in parentheses under the "species" entry of the table, as shown below.

Species

Rat
(Wistar)

The strain should not appear in the LSE figure.

Cancer

When cancer is the endpoint, plot the lowest exposure levels associated with increased tumors in experimental or epidemiological studies; these are termed CELs, rather than LOAELs. *Note: In some cases, it may be appropriate to use levels that are NOT statistically significant, because the resolving power of the study may be insufficient to capture cases where tumors are historically rare. Discuss this fact with the chemical manager.* Do not include NOAELs for cancer, either in the LSE table or the LSE figure, although doses not causing measurable cancer increases should be mentioned in the text. When providing CELs in an LSE table, include the cancer effect(s), e.g., 25 (CEL: liver tumors), 10 (CEL: acute myelogenous leukemia).

If different cancer effects were observed at levels higher than the lowest CEL, both levels and effects should be included in the table. List the lower CEL first.

10 (CEL: lymphoma)
50 (CEL: oral cavity tumor)

Also plot the range associated with the upper bound for an individual lifetime cancer risk of 10^{-4} to 10^{-7}, as derived by EPA's Human Health Assessment Group through the q_1^* methodology. Label this range "Estimated Upperbound Human Cancer Risk Levels" (see LSE figures, Exhibit 12). In some cases, EPA has extrapolated q_1^*s from one route to another. In other cases, such extrapolations have not been made. Plot the ranges for the second and third routes of exposure if and only if EPA has done the extrapolation. ***Contractors should not derive q_1^*s on their own.***

Specific Guidance for LSE Figures

At the bottom of each page of each LSE figure, provide a key to the LSE figure "2," "3," etc.

Next to each point plotted on the LSE figure, indicate the following information.

- The number of the study as shown in the corresponding LSE table.
- Species, using the following abbreviations. (Abbreviations used in the figure should be listed in the key in this order)

k = monkey
r = rat
m = mouse
g = guinea pig
s = hamster
d = dog
c = cat
h = rabbit ("hare")
p = pig
f = ferret
n = mink
a = sheep
e = gerbil
c = cow
x = chicken
j = pigeon
o = other

The key should show effects, using the following symbols.

Squares for LD_{50} or LC_{50} values
Circles for data from animals
Triangles for data from humans
Half-filled symbols for LOAELs for "less serious" effects
Black symbols for LOAELs for "serious" effects
Open symbols for NOAELs
Black diamonds for CELs in animals
Black inverted triangles for CELs in humans
MRL symbols

Vertically align dots in LSE figures to clarify existing dose-response relationships for a particular species and to group effects appropriately (e.g., a LOAEL should be above the corresponding NOAEL).

When CELs are presented in the LSE figure, place an asterisk on the "Cancer" heading and add the following footnote to the key of the figure.

> ***Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.**

See the sample LSE tables and figures in Exhibits 10, 11, and 12 for illustrations of the content and the appearance of these items.

Relationship Between LSE Tables/Figures and Profile Text

The text should not simply repeat information in LSE tables. Rather, the text should focus on a weight-of-evidence evaluation of whether the effect does or does not occur in humans or animals. ***All studies in LSE tables and figures should be discussed (or at least referred to, if the substance is data-rich) in the text.*** Discussion should include any reliable studies that provide qualitative data but were not included in the LSE table due to lack of quantitative data. The identified limitations should be included in the text and the supplemental document. Epidemiological studies and case reports often fall into this category. For data-poor substances, include a discussion of the strengths and weaknesses of the available data on a study-by-study basis. For data-rich substances, provide a more general discussion of the strengths and limitations of the available data, presenting an overall sense of the weight of evidence. Discuss whether different data sets are quantitatively similar, or whether NOAEL and LOAEL estimates vary widely between studies or species. If estimates vary widely, discuss likely or possible reasons.

In the text, refer to the LSE table and/or figure in each effect section. Use the following boilerplate at the beginning of the section on systemic effects and at the end of all other sections for which there are data in the LSE table.

> **The highest NOAEL values and all LOAEL values from each reliable study for (endpoint) in each species and duration category are recorded in Table 3-___ and plotted in Figure 3-___.**

When used, this statement should be modified to reflect the values accurately.

Note: In the Systemic Effects section, reference to the LSE table and figure often follows the introductory statement on the categories for which no studies were located. When this occurs, use a transitional statement, e.g., "The systemic effects observed after oral exposure are discussed below." The next sentence should refer to the tables.

Relationship Between LSE Tables/Figures and Profile Text for MRLs

Each data point used to derive an MRL is marked with a dashed line and an anchor symbol in the LSE figure and with a footnote in the LSE table. The footnote should use language patterned after the following examples.

- Example 1COral LOAEL in animals where dose has been adjusted for _____ intermittent exposure:

  Used to derive an intermediate oral minimal risk level (MRL) of ___ mg/kg/day; dose adjusted for intermittent exposure and divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

- Example 2CInhalation NOAEL in humans where dose has been adjusted for intermittent exposure:

  Used to derive an acute inhalation minimal risk level (MRL) of ___ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 10 (for human variability).

- Example 3CInhalation NOAEL in animals:

  Used to derive a chronic inhalation minimal risk level (MRL) of ___ ppm; dose converted to an equivalent concentration in humans and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

If more than one footnote for MRLs exists in a table, only spell out minimal risk level (MRL) the first time the phrase is used; thereafter, use the abbreviation.

The MRL should also be explicitly described in the appropriate location in the text, using language patterned after the following.

> **Based on this value, an acute oral MRL of 10 mg/kg/day was calculated as described in the footnote to Table 3-2 and in Appendix A.**

Classification of Endpoints as NOAELs and Less Serious and Serious LOAELs

The judgment of whether an endpoint is a NOAEL or a LOAEL depends in part upon the toxicity that occurs at other doses in the study or in other studies, and in part upon knowledge regarding the mechanism of toxicity of the substance. ATSDR defines the term "adverse health effect" in its Biennial Report, Volume II, to the Assistant Secretary for Health, U.S. Public Health Service: "a harmful or potentially harmful change in the physiologic function, physiologic state, or organ structure that may result in an observed deleterious health outcome [which] may be manifested in pathophysiologic changes in target organs, psychiatric effects, or overt disease." This definition is interpreted to indicate that any effect that enhances the susceptibility of an organism to the deleterious effects of other chemical, physical, microbiological, or environmental influences should be considered adverse.

All LOAELs should be identified in LSE tables and figures as "less serious" or "serious." In general, a dose that evokes failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death) is referred to as a serious LOAEL. For additional assistance regarding differences between less serious and serious effects, refer to "Guidance for the Derivation of MRLs," which appears later in this section. ATSDR acknowledges that a considerable amount of judgment is required in this process and that, in some cases; there will be insufficient data to decide whether or not an effect will lead to significant dysfunction. The chemical manager can help decide such questions by bringing knowledge of ATSDR's policies to the discussion. The distinction between less serious and serious is intended to help the users of the document see at what levels of exposure "major" effects begin to appear, and whether the less serious effects occur at approximately the same levels as serious effects or at substantially lower levels of exposure. ATSDR recognizes the difficulties in the use of LOAELs for this

purpose, particularly when species and dosing regimens are different and the doses are displayed as administered doses rather than absorbed doses. Nonetheless, ATSDR believes that there is sufficient merit in the approach to warrant an attempt at distinguishing between less serious and serious effects. The classification of an effect as less serious or serious is also important because the Agency's practice is not to derive MRLs from serious LOAELs.

When assessing the relevance (to humans) of observed effects, be aware of lesions that may be species related (e.g., nephropathy and renal tumors in the male rat associated with alpha$_{2u}$-globulin; spontaneous disorders such as chronic progressive nephropathy in the rat; the typically high incidence of mammary fibroadenoma in the rat; nodular hyperplasia of the adrenal cortex, liver, and spleen in aging dogs; the extramedullary hematopoiesis that may normally persist throughout the life of mice).

The following classification scheme provides more definitive guidance for the development and standardization of supplemental document and LSE tables and for the derivation of MRLs.

No Adverse Effects

- Weight loss or decrease in body weight gain of less than 10%.

- Changes in organ weight of non-target organ tissues that are not associated with abnormal morphologic or biochemical changes (see guidance on "Assessment of Organ Weight Change").

- Increased mortality over controls that is not significant ($p>0.05$).
- Some adaptive responses (see guidance on "Assessment of Hepatic Adaptive Responses").

Less Serious Effects

- Reversible cellular alterations at the ultrastructural level (e.g., dilated endoplasmic reticulum, loss of microvilli, myelin figures) and at the light-microscopy level (e.g., cloudy swelling, hydropic degeneration, fatty change).
- Necrosis (dependent upon location, distribution, and magnitude), metaplasia, or atrophy with no apparent decrement of organ function.
- Serum chemistry changes (e.g., moderate elevations of SGOT, SGPT).

- Organ weight change in known target organ tissue that is not associated with morphologic or biochemical alterations (see "Assessment of Organ Weight Change").
- Weight loss or decrease in body weight gain of 10-19% (assuming normal food consumption).
- Some adaptive responses (see "Assessment of Hepatic Adaptive Responses").

Transitional Effects (Between Less Serious and Serious)

Note: Some effects (such as necrosis, atrophy, metaplasia, and serum chemistry alterations) could be classified as less serious or serious based on their reversibility, the organ affected, or the degree of associated dysfunction.

Serious Effects

- Death.
- Clinical effects of significant organ impairment (e.g., convulsions, icterus, cyanosis).
- Morphologic changes in organ tissues that could result in severe dysfunction (e.g., marked necrosis of hepatocytes or renal tubules).
- Weight loss or decrease in body weight gain of 20% or greater (assuming normal food consumption).
- Serum chemistry changes (e.g., major elevations of SGOT, SGPT, BUN).
- Major metabolic effects (e.g., ketosis, acidosis, alkalosis).
- Cancer effects.

To provide more specific guidance and encourage more consistent MRL derivation, seventeen system categories are presented below in greater detail. Effects within the system categories are also discussed below and classified as less serious or serious in Tables 3-1– 3-17. The LOAEL descriptor that appears in the LSE tables of the profile should be modeled after the terminology used in these tables. Avoid terms that are vague or nonspecific (e.g., CNS depression, EC_{50} for behavioral effects, and CNS toxicity).

System Categories: General Issues

The discussion within each effect category should focus on the primary site of attack of the substance or compound. Example: For neurological effects, are the effects more motor, sensory, or cognitive? Consider all effects in this regard, i.e., where did the effect occur? Always

indicate if the effects occurred only in animals that died. Maternal toxicity should always be indicated if it occurred in developmental studies.

When presenting human studies, include the cohort size, follow-up period, and the incidence of the effects. The incidence of effect and/or severity should also be mentioned in the text for animal and human studies wherever confusion could arise regarding the interpretation of concentration or dose responses (e.g., if a concentration or dose response is noted in the text but not in the table, provide the evidence).

Death

- The section under "death" should address whether increased mortality has been observed in human or animal studies and, if so, what was the cause of death. If from cancer in human studies, state that retrospective mortality studies associating exposure with cancer are discussed in Section 3.2._._.

- Deaths should always be classified as "serious LOAELs" and NOAELs are not used. If an article does not provide data on the mortality of animals, do not discuss this article in the death section. If an article provides data regarding the mortality of animals and no animals died, this can be discussed as "no deaths occurred." For studies which provide a range for an LD_{50}, the lowest dose should be used for the LSE table and figure LOAEL (do not put in ranges).

Systemic Effects

Assessment of Organ Weight Change. Organ weight change is considered to be an adverse effect if observed in a known target organ. For the purpose of MRL derivation, organ weight change in a known target tissue is considered as a minimal LOAEL (uncertainty factor of 3 applied) if the response is associated with no other alterations (morphologic, biochemical); organ weight change in this case may be representative of early-stage adverse effects. Increased liver weight following exposure to known hepatotoxins is a good example of such an effect. Changes in the organ weight of nontarget organ tissues that are not associated with morphologic or biochemical alterations are not considered to be adverse effects.

Increased lung weight may be the result of pulmonary edema. In this case, the effect would not be treated as minimal. Similarly, decreased organ weight may be associated with severe atrophy with resulting deterioration of organ function (e.g., testicular, ovarian, or thymic atrophy). In assessing the nature and significance of changes in organ weight, use data provided in the study along with sound scientific judgment.

LOAELs should not be based on changes in absolute organ weight in the absence of body weight information. If body weight information is provided and there are no body weight effects, either absolute or relative organ weight changes can be used as the basis for LOAELs.

If body weight is reduced, then a decrease in absolute organ weight could reflect a body weight reduction or it could be an effect all by itself. If relative organ weight is not provided, do not base a LOAEL on absolute organ weight change unless other supporting data is provided; if relative organ weight is provided and it is significantly decreased, then decreased absolute organ weight may be used for a LOAEL. If body weight is reduced and absolute organ weight is increased, then this increase is probably real (and may be used as a LOAEL). If absolute organ weights do not differ, but there is dose-related decrease in body weight, then there would appear to be an increase in relative organ weight in the treated group; do not report a LOAEL for the increased relative weight. Changes in body weight, absolute organ weight, and relative organ weight all need to be assessed before it can be decided whether an organ weight change is real.

Maternal Effects. Systemic effects (as well as immunological/lymphoreticular, neurological, death, or cancer) which occurs in the dam should be discussed under their respective effect categories, rather than under "reproductive." However, it should be clearly stated in the discussion that these effects occurred to the dam (e.g., "decreased maternal body weight gain" or "convulsions in dams", etc.).

Dose-response and LOAELs. If an adverse effect occurs at all dose levels, but it is only statistically significant at the low dose (and not the high dose), scientific judgment must be used to determine if the lowest dose should be considered a LOAEL. If all dose levels significantly affect an endpoint, but there is no clear dose-response relationship, the lowest dose level might

be a LOAEL. It is possible that a lower incidence of intensity of effects (such as cancer or other histopathological lesions) at the high dose is due to increased mortality at the high dose and more animals may have developed the lesion had they lived, or the maximum response was already achieved with the lowest dose level. It is also possible that the effect may be due to a saturated enzyme or pathway at the high dose, or the effect could be a spurious result.

Adaptive responses are generally considered to be effects that enhance an organism's performance as a whole and/or its ability to withstand a challenge (i.e., homeostatic mechanisms). However, the boundary between an adaptive and toxic response is not always well delineated. Adaptive responses in effect may result in changes that are beneficial or potentially detrimental to the host. Hypertrophy of skeletal muscle in response to an increased work load is an example of an adaptive change that would be expected to prove beneficial to the host. Metaplasia may be considered an adaptive response, but the predictive value for lesion progression and secondary effects on other organs is not always clear. The morphologic term metaplasia does not give any information concerning the biological significance of such a change. If metaplasia occurs in the pancreasCfor example, squamous metaplasia of pancreatic ducts associated with exposure to a test substanceCit does not interfere with pancreatic function. However, if squamous metaplasia occurs in the tracheal epithelium, it may interfere with normal respiratory defense functions. Therefore, assessment of the biological significance of an adaptive response is most appropriately made on a case-by-case basis in conjunction with the Chemical Manager.

Respiratory Effects

Respiratory effects include any effects related to the respiratory system and its functioning. This includes effects to the lung, trachea, and nasal cavity. Examples of specific respiratory effect endpoints are listed and classified as less serious or serious in Table 3-1.

Table 3-1. Respiratory Effect Endpoints

Effect	Less Serious	Serious

Tachypnea (rapid, shallow respiration)	+	+
Dyspnea (labored breathing)	+	+
Wheezing	+	
Pulmonary edema		+
Altered lung function (changes in respiratory volume, forced vital capacity, etc.)	+	
Lung congestion	+	
Lung or nasal irritation	+	
Hemothorax (blood in the pleural cavity)		+
Bronchitis	+	+
Rales (abnormal respiratory sounds)		+

Cardiovascular Effects Cardiovascular effects include any effects related to the heart and circulatory system and its functioning. Examples of specific cardiovascular effect endpoints are listed and classified as less serious or serious in Table 3-2.

Table 3-2. Cardiovascular Effect Endpoints

Effect	Less serious	Serious
Altered blood pressure (increased or decreased)	+	+
Bradycardia (slowed heart beat/pulse)	+	+
Tachycardia (excessively rapid heart beat)	+	+
Cardiac arrest		+
Myocardial edema		+

Myocarditis		+
Altered prothrombin time	+	
Palpitations	+	+

Gastrointestinal Effects

Gastrointestinal effects include any effects related to the digestive system. This includes effects on the esophagus, stomach, and small and large intestines. Some pancreatic effects are reported as gastrointestinal (see Endocrine Effects below). Examples of specific gastrointestinal effect endpoints are listed and classified as less serious or serious in Table 3-3.

Table 3-3. Gastrointestinal Effect Endpoints*

Effect	Less serious	Serious
Diarrhea*	+	
Emesis (vomiting)	+	
Ulceration		+
Constipation	+	
Nausea	+	

* For diarrhea and emesis, these effects could be serious if they occur for a long length of time

Hematological Effects

Hematological effects include effects related to blood chemistry and hematology. Examples of specific hematological effect endpoints are listed and classified as less serious or serious in Table 3-4.

Table 3-4. Hematological Effect Endpoints

Effect	Less serious	Serious
Anemia	+	+
Cyanosis	+	
Erythrocytopenia (erythropenia)	+	+
Altered hemoglobin (increased or decreased)	+	
Altered hematocrit (increased or decreased)	+	
Leukopenia		+
Thrombocytopenia		+
Increased erythrocytes	+	+
Bone marrow hyper or hypoplasia	+	
Decreased bone marrow cellularity	+	

Musculoskeletal Effects

Musculoskeletal effects are those related to the muscles and skeletal system and its functioning. Examples of specific musculoskeletal effect endpoints are listed and classified as less serious or serious in Table 3-5.

Table 3-5. Musculoskeletal Effect Endpoints

Effect	Less serious	Serious
Loss of muscle tone or strength	+	

Muscular rigidity		+
Muscular atrophy		+
Arthritis	+	
Altered bone density	+	
Arthralgia (joint pain)	+	

Hepatic Effects

Hepatic effects are those related to the liver and its functioning. Additionally, effects to the gallbladder should be discussed under "hepatic effects."

In the liver, exposure to many substances may result in adaptive changes that are characterized by induction of the mixed function oxidase enzyme system and proliferation of smooth endoplasmic reticulum; other changes that may be observed include hepatocellular hypertrophy, cytoplasmic eosinophilia, increased organ weight, and liver enlargement. Modifications occurring in the mixed function oxidase system as a consequence of the adaptive response may potentiate or inhibit toxic responses to other exogenous substances. Agents that induce chemical metabolizing enzyme systems generally tend to potentiate hepatic injury produced by compounds such as chloroform, carbon tetrachloride, or halothane. For ATSDR, this is an especially important concept to consider because, in addition to the specific chemical causing adaptive changes, there is the potential for exposure to many other substances at NPL sites.

The borderline between adaptive physiology and toxicity (functional impairment) is not always well delineated. The following guidance provides general direction for assessing hepatic adaptive responses; although this guidance will be appropriate in most cases, there may be exceptions. However, for the purpose of assessing the biological significance of adaptive responses in the liver, the following criteria should be used: Biochemical changes characterized by induction of enzymes of the mixed function oxidase system along with morphologic changes of hepatocellular hypertrophy and proliferation of smooth endoplasmic reticulum should be

considered potentially adverse and should be classified as a less serious LOAEL. Other supportive changes that may be observed include increased organ weight, hepatic enlargement, and accentuated cytoplasmic eosinophilia. To maximize the accuracy of assessing hepatic (or other) adaptive responses, in addition to the guidance given here, this interpretive process must be accompanied by insightful case-by-case analysis.

Examples of specific hepatic effect endpoints are listed and classified as less serious or serious in Table 3-6

Table 3-6. Hepatic Effect Endpoints

Effect	Less serious	Serious
Altered liver enzymes	+	
Hepatomegaly (enlargement of the liver)	+	
Porphyria (disturbance of porphyrin metabolism)	+	
Hepatocyte vacuolization	+	
Congestion of liver	+	+
Hepatic necrosis		+
Cirrhosis		+
Jaundice	+	
Gall bladder effects	+	+
Fatty changes in liver	+	+
Hepatocellular degeneration	+	+

Renal Effects

Renal effects include any effects related to the kidneys and their functioning. Additionally, effects to the urinary bladder should be discussed under Arenal effects.@

Interpretation of Renal Pathology in the Male Rat. ***The chapter-specific guidance given here must be read in conjunction with Attachment G (Interpreting Renal Pathology in the Male Rat).***

Alpha$_{2u}$-Globulin Induced Renal Pathology in Male Rats. Nephropathy and renal tumors associated with chemicals that induce accumulation of α_{2u}-g appear to be unique responses of the male rat. Therefore:

- Nephropathy in the male rat that is associated with α_{2u}-g accumulation should not be used as an endpoint for quantitative non-carcinogenic risk assessment (MRL derivation).

- Renal tubule tumors in the male rat that are associated with α_{2u}-g accumulation should not be used to support qualitative weight of evidence that a chemical poses a cancer risk in humans; these endpoints also should not be used for dose-response extrapolations that estimate human cancer risk.

Kidney effects data related to α_{2u}-g accumulation in the male rat should be discussed in the profile and included in the LSE tables (even though it may not be used for MRL derivation). However, the association of renal lesions to α_{2u}-g accumulation and the relevance (or irrelevance) of these endpoints to risk assessment (human extrapolation) should be clearly discussed.

Chronic Progressive Nephropathy. Chronic progressive nephropathy (CPN) in the aging male rat can complicate the interpretation of other renal lesions. However, nephropathy in the male rat that is not attributable to either CPN or α_{2u}-g accumulation may provide endpoints that are suitable for consideration in the risk assessment process, particularly if similar effects are seen in female rats, mice, or other species. Lesions related to CPN in exposed rats should not be used as endpoints in quantitative risk assessment (MRL derivation), with some exceptions. Lesions of

CPN in exposed rats may be considered as potential endpoints for estimating noncarcinogenic risk if exposed male and female or only female* rats have CPN lesions that exhibit a clearly defined dose response. More specifically, with increasing exposure doses there should be a progressive significance of CPN lesions as characterized by (1) an earlier age of onset, (2) increasing severity, (3) an increased frequency of animals affected. (One or any combination of these three items may be present.) Observation of renal effects in other similarly exposed species contributes to the weight of evidence in these cases.

In cases where the above criteria are met, NOAEL values for lesions of CPN can be considered for quantitative risk assessment. A NOAEL in this situation is defined as a test dose that produces no statistically significant enhancement of CPN lesions compared with the controls. The effect description for NOAEL values should read "no enhancement of CPN in females" (and males, if appropriate). At those doses where enhancement of CPN lesions is observed, effects should be classified as less serious LOAELs or serious LOAELs, depending upon their magnitude. Less serious LOAEL values can be considered for MRL derivation if NOAELs have not been identified. The effect description for LOAEL endpoints should read, "dose-related enhancement of CPN in females" (and males, if appropriate).

Examples of specific renal effect endpoints are listed and classified as less serious or serious in Table 3-7.

Table 3-7. Renal Effect Endpoints

Effect	Less serious	Serious
Fatty degeneration of tubules	+	
Altered blood urea nitrogen (BUN)	+	
Urinary bladder effects	+	+

*In untreated rats, CPN is typically much more severe in males. If exposed females exhibit a dose response, such a pattern may be obscured in the exposed male rat due to the severity of the lesion.

Altered urinary creatinine	+	
Proteinuria (excess of serum proteins in urine)	+	
Renal tubular degeneration	+	+
Decreased urine volume (not associated with decreased water intake)	+	
Hematuria		+
Hemoglobinuria		+
Renal tubular casts	+	
Tubular necrosis	+	+

Endocrine Effects

Endocrine effects involve ductless hormone-secreting glands that includes the hypothalamus, pituitary gland, adrenal glands (including the adrenal cortex and medulla), thyroid glands, parathyroid glands, and the pancreatic islets. Examples of endocrine effects include adrenal cortical atrophy, pituitary hypoplasia, thyroid hyperplasia, and adrenal calcification. Functional changes involving hormonal deficiency or excess (e.g., deficiency of T_4 and T_4 [hypothyroidism], excess of cortisol [hyperadrenocorticism], and excess parathyroid hormone [hyperparathyroidism]) also fall in this category. Although the ovaries and testes have endocrine functions, for reasons of consistency always categorize effects involving these organs as reproductive effects.

The pancreas is both an endocrine and an exocrine organ. As an exocrine organ, it is considered to be part of the digestive system (secretion of digestive enzymes via the pancreatic duct into the duodenum), and as an endocrine organ (secretion of insulin) it is an endocrine organ (obviously). The pancreas should be discussed under "Endocrine Effects" unless it is known that the effect involves the external secretions of digestive enzymes; under those circumstances, it would be discussed under "Gastrointestinal Effects."

Examples of specific endocrine effect endpoints are listed and classified as less serious or serious in Table 3-8.

Table 3-8. Endocrine Effect Endpoints

Effect	Less serious	Serious
Alternations of serum adrenocorticotropic hormones	+	+
Decreased thyroid, pituitary or adrenal function	+	
Goiter (enlargement of thyroid gland)	+	
Pituitary hypoplasia	+	+
Thyroid hyperplasia	+	+
Adrenal calcification	+	+
Pancreas effects	+	+
Adrenal cortical atrophy	+	+

Dermal Effects

Dermal effects include those related to the skin and its functioning. It should be noted that while dermal sensitization could be considered both an immunological effect and a dermal effect, it should be addressed under "dermal effects" and cross referenced to immunological effects. Sensitization reactions and the mechanism of the allergic response should then be further discussed.

Where dermal effects are noted upon exposure to a substance in air and where these effects are not considered to be true systemic effects but due to the direct action of the substance (i.e., irritation) on the skin, these effects should be mentioned briefly under inhalation and further elaborated under dermal exposure. State under the inhalation section that the effects were due to

direct contact of the skin with the vapor and that other dermal effects resulting from direct contact are mentioned in Section 3.2.3. The data should then be presented in the dermal LSE table. Reference to the study in the dermal section should clearly state that the animal was exposed to the substance via air.

Examples of specific dermal effect endpoints are listed and classified as less serious or serious in Table 3-9.

Table 3-9. Dermal Effect Endpoints

Effect	Less serious	Serious
Dermatitis	+	
Edema (swelling)	+	
Erythema (redness of skin)	+	
Hyperkeratosis (hypertrophy of corneous layer of skin)	+	
Ulceration	+	
Itching	+	
Rash	+	
Acne	+	
Necrosis of skin	+	+
Acanthosis (diffuse hyperplasia and thickening of prickle-cell layer of epidermis)	+	

Ocular Effects

Ocular effects are those related to the eyes and their functioning. Examples of specific ocular effect endpoints are listed and classified as less serious or serious in Table 3-10.

Table 3-10. Ocular Effect Endpoints

Effect	Less serious	Serious
Blindness		+
Cataracts		+
Myopia (nearsightedness)	+	
Lacrimation/tearing	+	
Exophthalmia		+
Conjunctivitis	+	
Irritation	+	
Discharge or exudate	+	

Body Weight Effects

Body weight effects are changes in terminal body weight and changes in body weight gain for adult animals (in a non-reproductive study). The NOAEL and LOAEL would be based upon significant differences in terminal body weight between controls and treated animals. In a reproductive study, discussing changes in maternal body weight gain is appropriate. Weight loss or decreased body weight of 10-19% (assuming normal food consumption) is to be classified as a "less serious LOAEL" and decreases of 20% or more are to be classified as a "serious LOAEL" (see Table 3-11); a body weight decrease of less than 10% is not considered to be adverse effect. If a decrease in body weight is accompanied by decreased food consumption in a feeding study, then neither effect is considered an adverse effect.

Table 3-11. Body Weight Effect Endpoints

Effect	Less serious	Serious
Decreased body weight (10–19%) with normal food consumption	+	
Decreased body weight (> 20%) with normal food consumption		+

Metabolic Effects

Metabolic effects include disturbances in acid-base balance. The type and cause of the abnormality should be distinguished, and these findings then correlated with the laboratory results, clinical signs, and morphologic changes presented in the study. Essential to the interpretation of metabolic effects is sound knowledge of the biomedical field. Other states that should be discussed as Ametabolic effects@ include water depletion and water excess, hyper- and hyponatremia, hyper- and hypokalemia, hyper- and hypocalcemia, hyper- and hypomagnesemia, hyper- and hypophosphatemia, ketosis, hyperglycemia, hyperuricemia, increased osmolal gap, and so on. The pH of extracellular fluid (ECF) in healthy individuals, which ranges between 7.35 and 7.45, is maintained by the equilibrium between H^+ and HCO_3- levels in the body. Metabolic acidosis represents a primary fall in ECF bicarbonate concentration; both blood pH and HCO_3- levels are reduced. Respiratory acidosis involves a primary increase in arterial carbon dioxide pressure; blood pH decreases and HCO_3- concentrations increase if renal function is intact. Metabolic alkalosis is defined as a primary increase in blood bicarbonate levels; blood pH and HCO_3- levels are both elevated. Respiratory alkalosis involves a primary decrease in carbon dioxide pressure; blood pH rises and HCO_3- levels fall.

Examples of specific metabolic effect endpoints are listed and classified as less serious or serious in Table 3-12.

Table 3-12. Metabolic Effect Endpoints

Effect	Less serious	Serious
Acidosis or alkalosis		+
Altered body temperature (hyper or hypothermia)	+	+
Altered perspiration	+	+
Ketosis, hyper or hypo: glycemia, uricemia, atremia, kalemia, calcemia, magnesemia, phosphatemia, etc.		+
Increased osmolal gap		+
Altered oxygen consumption	+	
Altered metabolic rate	+	+

Other Systemic Effects

The Aother systemic effects@ category includes a wide variety of systemic effects that do not fit into the other categories listed above. Examples of some of these effects are listed in Table 3-13.

Table 3-13. Other Systemic Effect Endpoints

EFFECT	Less Serious	Serious
Altered water consumption	+	
Altered food consumption	+	
Alopecia	+	
Fur discolorations	+	

Hirsutism (abnormal hairiness)	+	

Immunological and Lymphoreticular Effects

The immune system is a cellular complex that forms the basis of the body's defenses against both biological and chemical exogenous substances. Lymphoreticular effects are morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus. Cells that mature or reside in these tissues, such as various populations of lymphocytes and nonlymphoid cells (phagocytes), participate in immune responses. Nevertheless, lesions involving these tissues *may* or *may not* be associated with functional changes in the immune response. Examples of lymphoreticular effects are lymphoid aplasia of the thymus, lymphoid hypoplasia of the lymph nodes, lymphoid hyperplasia of the spleen, hemosiderosis of the spleen, and lymph node histiocytosis. Immunological effects, in contrast, are functional changes in the immune response. These include a broad spectrum of effects, such as anaphylaxis, decreased cell-mediated immunity, autoimmunity, altered complement activity, altered T-cell activity, decreased mitogen response, and increased susceptibility to infection.

When a substance is identified as an immunotoxicant, sufficient supportive information must be provided. Many substances have been identified that impart an immunological effect for multiple routes and/or durations of exposure. Only after a thorough investigation of the toxicological information in animals can an assessment be made concerning potential immunological effects in humans.

Immunological and lymphoreticular effect endpoints are listed and classified as less serious or serious in Table 3-14.

Table 3-14. Immunological and Lymphoreticular Effect Endpoints

Effect	Less serious	Serious
Altered complement activity	+	
Altered macrophage activity	+	

Effect	Less serious	Serious
Altered resistance to tumor susceptibility by sarcoma virus	+	
Altered T-cell activity	+	
Chronic urticaria	+	
Decrease in lymph node cortical lymphoid cells[a]	+	
Decreased mitogen response	+	
Decreased skin graft survival time	+	
Degeneration or necrosis in immunologic components		+
Delayed rejection time of foreign skin graft (non-self)	+	
Enhanced natural killer cell (N.C.) activity	+	
Humoral or cell-mediated immune response to sheep red blood cells	+	
Increased susceptibility to infection	+	
Pemphigus vulgaris		+
Reduced delayed-type hypersensitivity	+	
Reduced humoral antibody (I.G.) production	+[b]	+
Severe reduction in cell-mediated immune response		+
Suppression of lymphoproliferative response to T-cell mitogen	+	
Thymus or spleen lymphoid atrophy[a]		+
Lymphoid hyperplasia of lymph node or spleen[a]	+	
Histiocytosis of lymph node or spleen[a]	+	

[a] These changes are lymphoreticular effects because they represent morphological alterations in affected tissues; immunological effects imply a functional change in the immune response. Lymphoreticular effects may or may not be associated with functional changes in the immune response. If morphological changes are present in lymphoreticular tissues, the possible association with functional alterations should be addressed.

[b] The effect can be less serious or serious depending upon the degree.

Neurological Effects

Neurotoxicity is any adverse effect on the structure or function of the central or peripheral nervous system by a biological, chemical, or physical agent. Neurologic effects may be permanent or reversible, produced by neuropharmacological or neurodegenerative properties of a neurotoxicant, or the result of direct or indirect actions on the nervous system. Neurological effects can be categorized as motor, mood and personality, sensory, cognitive, neurochemical, neurophysiologic, or neuropathologic. Examples of specific endpoints within these effect categories are listed and classified as less serious or serious in Table 3-15.

Assessment of Acetylcholinesterase Activity Inhibition. (See Attachment H – Assessing Cholinesterase Activity Inhibition) In classifying the neurological health-effect endpoint of "inhibition of acetylcholinesterase activity" (in erythrocytes and/or brain), the following guidelines should be followed: 20–59% inhibition of enzyme activity is classified as a less serious LOAEL; enzyme activity inhibition of 60% or greater is classified as a serious LOAEL. However, in addition to these guidelines, consideration should be given to associated clinical symptoms (see Table 3-15b). If clinical effects observed at a particular exposure level are most consistent with those symptoms described in the table under moderate or severe poisoning, this exposure level should be classified as a serious LOAEL, even if the degree of inhibition of acetylcholinesterase activity is less than 60%. In those cases where inhibition of enzyme activity of less than 60% is classified as a serious LOAEL, the specific clinical effects that lead to this classification (as well as the percentage of enzyme inhibition) should be clearly stated in the text of Chapter 3 and in the LSE tables. Inhibition of acetylcholinesterase activity of 60% or greater should always be classified as a serious effect. It is not appropriate to base LOAELs on the inhibition of pseudocholinesterase activity (plasma or serum cholinesterase), but this effect

should be discussed under Aresults of study@ in the text of the supplemental document. Inhibition of erythrocyte acetylcholinesterase should be discussed under neurological effects and not hematological effects.

Table 3-15a. Neurological Effect Endpoints

Effect	Less serious	Serious
MOTOR		
Activity changes (sedation, anesthesia, somnolence, hyper-/hypoactivity, decreased locomotor activity)	+[b]	+
Convulsions		+
Lack of coordination (unsteadiness, intoxication, decreased swimming response ability, decreased psychomotor performance, ataxia)	+[b]	+
Paralysis		+
Reflex abnormalities	+[b]	+
Tremor, twitching (muscular spasm)		+
Weakness	+	
MOOD AND PERSONALITY		
Excitability	+	
Delirium		+
Depression	+[b]	+[b]
Hallucinations		+
Irritability	+	
Nervousness, tension	+	
Restlessness	+	
Sleep disturbances	+	
SENSORY		
Auditory disorders		+
Equilibrium changes	+[b]	+
Pain disorders	+[b]	+
Tactile disorders	+[b]	+
Vision disorders		+
COGNITIVE		
Confusion		+

Effect	Less serious	Serious
Learning impairment (decreased operant behavior)	+[b]	+
Memory problems		+
Speech impairment		+
GENERAL		
Depression of neuronal activity	+[b]	+
Fatigue (lethargy)	+	
Loss of appetite	+	
Narcosis, stupor		+
Nerve damage		+
Prostration		+
Other integrative effects (hand/eye coordination)	+[b]	+
Unconsciousness		+
NEUROCHEMISTRY		
cAMP or cGMP changes, catecholamine changes, dopamine changes, (decreased enzyme activity)	+[b]	+
Changes in GFA protein		+
Decreased neuronal membrane lipids	+[b]	+
Decreased metabolism (glucose utilization)	+[b]	+
NEUROPHYSIOLOGY		
Altered EEG	+[c]	+
Salivation	+	
NEUROPATHOLOGY		
(Peripheral neuropathy, demyelination, focal gliosis, cerebellar lesions, cerebellar degeneration, malacca, hemorrhage)		+

[a] Adapted from: Anger AW. 1986. Workplace exposures. In: Annau Z, ed. Neurobehavorial toxicology. Baltimore, MD: Johns Hopkins University Press, L331-347.

[b] Neurologic effects that could be less serious or serious must be described as "slight" or "severe," or by another adjective describing severity.

[c] No other clinical effects.

Table 3-15b. Neurological Effects: Clinical Symptoms of Varying Severity of Organophosphorus Poisoning and Corresponding ACHE[ta] Value[b]

Level of poisoning	Clinical symptoms
Mild <60% reduction of ACHE	Weakness, headache, dizziness, diminished vision, salivation, lacrimation, nausea, vomiting, lack of appetite, stomachache, restlessness, myosis, moderate bronchial spasm; convalescence in 1 day
Moderate 60–90% reduction of ACHE	Abruptly expressed general weakness; headache; visual disturbance; excess salivation; sweating; vomiting; diarrhea; Bradycardia; hyperopia; stomachache; twitching of facial muscles; tremor of hand, head, and other body parts; increasing excitement, disturbed gait, and feeling of fear; meiosis nystagmus; chest pain; difficult respiration; cyanosis of the mucous membrane; chest crepitation; convalescence in 1–2 weeks
Severe 90–100% reduction of ACHE	Abrupt tremor, generalized convulsions, psychic disturbances, intensive cyanosis of the mucous membrane, edema of the lung, coma; death from failure

[a] Acetylcholinesterase activity

[b] Adapted from: Kaloyanova FP, El Batawi MA. 1991. Human toxicology of pesticides. Boca Raton, FL: CRC Press, 3-57.

Reproductive Effects

Reproductive toxicity is defined as a dysfunction induced by a chemical, physical, and/or environmental agent that affects the process of gametogenesis from its earliest stage to implantation of the conceptus in the endometrium.

Examples of reproductive effect endpoints are listed and classified as less serious or serious in Table 3-16.

Table 3-16. Reproductive Effect Endpoints

Effect	Less serious	Serious
Abnormal sperm[a] (morphology, count, motility)		+
Abortions		+
Atrophy		+
Decreased fertility[b]	+	+
Decreased litters		+
Decreased spermatogenesis[a]	+	+
Degeneration of epididymides[b]	+	+
Disrupted spermatogenesis		+
Females: no reproduction		+
Maternal toxicity		+
Increased estrus		+
Irreversible histological change in testes		+
Ovarian dysfunction		+
Ovary weight change	+	
Postimplantation loss		+
50% reduction in number of offspring		+
Sterility		+
Testicular atrophy		+
Testicular degeneration	+	+
Granuloma epididymides[c]	+	+

Effect	Less serious	Serious
Tubular degeneration		+
Tubule edema	+	
Vaginal bleeding	+	

[a] There is a certain degree of variability between normal/less serious/serious; e.g., a normal human semen specimen has a volume of 3-4 mL, a sperm count of $30x10^6$, and 80% morphologically normal and motile spermatozoa.

[b] The effect can be less serious or serious depending upon the degree.

[c] This condition can be considered serious because it can lead to progressive fibrosis.

Reproductive effects that are also considered developmental should be mentioned under developmental effects as well, and they should be included in the LSE table with the other developmental effects. In a reproductive study, changes in maternal body weight gain should be presented as well as changes in body weight in males. Testicular effects can often be secondary to decreased body weight gain.

Developmental Effects

The Developmental Effects sections will include developmental health effects *on the offspring* resulting from exposures to: *parental germ cells* [formed when the parents were in utero], *the conceptus through the preBimplantation blastocyst stage*, and all subsequent developmental stages up through 18 years of age in humans or sexual maturity in animals. These Developmental Effects sections will discuss exposures that might result in developmental health effects *to the embryo or later stages of life*. Deaths at any stage before implantation will still only be discussed in the Reproductive Effects sections because such outcomes do not affect the health of the embryo, fetus, infant, child, adolescent, adult, or adult's offspring. The reason for this change in scope is recent research in animals showing that exposure of parental germ cells or preBimplantation conceptuses to certain mutagens can result in structural malformations in lateBstage fetuses and neonates, although these phenomena are often accompanied by an

expectedly high death rate in litter mates (Rutledge et al. 1992; Spielmann and Vogel 1989; Rutledge 1997; Generoso et al. 1990). In theory, either genetic or nonBgenetic damage (such as changes in DNA methylation or disruption of the expression of key developmental regulatory molecules) to the parental germ cells or the preBimplantation conceptus could result in functional or structural defects in the offspring. Mutations and childhood cancer are also theoretical outcomes of preBimplantation damage. Organogenesis is still considered the most susceptible period for the induction of structural malformations.

References:

Rutledge JC, Generoso WM, Shourbaji A, Cain KT, Gans M, and Oliva J. 1992. Developmental anomalies derived from exposure of zygotes and firstBcleavage embryos to mutagens. Mutation Research 296:167–177.

Spielmann H and Vogel R. 1989. Unique role of studies on preBimplantation embryos to understand mechanisms of embryotoxicity in early pregnancy. Critical Reviews in Toxicology 20:51–64.

Rutledge JC. 1997. Developmental toxicity induced during early stages of mammalian embryogenesis. Mutation Research 396:113–127.

Generoso WM, Rutledge JC, and Aronson J. 1990. Developmental anomalies: mutational consequence of mouse zygote exposure. Banbury Report 34: Biology of Mammalian Germ Cell Mutagenesis, Cold Spring Harbor Press.

Determining whether exposure causes developmental effects or just causes health effects during childhood is sometimes difficult. If this determination is unclear, discuss the effect either in a Developmental Effects section or the appropriate systemic toxicity section, with a crossBreference to the other section.

Topics marked by a closed bullet (●) must be discussed, if only to say that no information is available. Issues marked by a open bullet (○) should not be discussed if no relevant information is available.

- What health effects have been observed in children? Are there health effects observed in adults that are also of potential concern in children? What health effects have been observed in adults exposed as children? What health effects have been observed in immature animals from embryos up through maturity? Do children and immature animals exhibit the same types of health effects as adults? Do the doses that cause effects in children and adults or in immature and adult animals consistently differ? How? Consider any epidemiologic studies that focus on the consequences of exposures before age 18 years, even if the effects are not evident until adulthood.

- Is the developmental process altered by the toxicant? Discuss data on children and animals. [Remember that in vitro developmental models and in vivo developmental effects from exposures other than inhalation, oral, or dermal are discussed in Chapter 2 **Relevance to Public Health**.] Remember that the reproductive, immune, and nervous systems especially continue to develop after birth. Developmental problems may include functional neurological development, such as learning deficits and deficits in social behavior. Consider endocrine disruption of developmental processes and any epidemiologic studies that focus on the consequences of exposures before age 18 years, even if the effects are not evident until adulthood. If the developmental process is altered by the toxicant, how does the effective dose or range of effective doses in children compare with that in adults? If developmental effects only occur near maternally toxic doses, this point should be discussed. Assistance in interpreting developmental studies can be found in: **Attachment I: Age at weaning and sexual maturity for common laboratory species and humans** and **Attachment J: Historical background rates for various developmental outcomes used in interpreting National Toxicology Program (NTP) developmental studies on rabbits, rats, and mice**.

o Are there any studies linking preBconception exposure of either parent to germ line mutations, developmental defects, childhood cancer, or other health effects?

Developmental toxicity is any adverse effect on the developing organism from implantation, through prenatal development, or postnatally to the time of sexual maturation. These effects can result from exposure of either parent prior to implantation or exposure during prenatal and postnatal development. Systemic, immunological, or neurological effects seen in the developing organism prior to sexual maturity may be considered secondary to adverse developmental effects.

Developmental effects are distinguished from reproductive effects by evaluation of the conceptus after it is implanted. (Reproductive toxicity is defined as dysfunction induced by a chemical, physical, or biologic agent that affects the processes of gametogenesis from its earliest stage to implantation of the conceptus in the endometrium.

Developmental effects can be categorized as structural abnormalities, altered growth, functional deficiencies, and death of the developing organism. Examples of specific endpoints within these effect categories are listed and classified as serious or less serious in Table 3-17.

Structural abnormalities include malformations and variations, which also may be referred to as anomalies, deformations, or aberrations. The term "teratogenicity" is used to describe permanent structural abnormalities that may adversely affect survival, development, or function.
Altered growth can be induced at any stage of development, may be reversible, or may result in permanent change. Changes in the mother (dam or doe) can influence or confound interpretation of altered growth in the fetus or neonate. In general, altered growth seen in conjunction with adverse effects in dams, such as decreased weight gain has been treated as an adverse effect in the fetus or neonate.

Adverse effects observed in offspring (exposed *in utero*) prior to sexual maturity are considered to be developmental effects. Mice and rats are weaned at about 21–28 days and then there is a juvenile phase that follows. Full sexual maturity is assumed to occur several weeks after weaning (at about 60–70 days). Effects noted in the juvenile phase after pre- and postnatal exposure is still considered to be developmental effects. For example, if animals were exposed *in utero* and are then allowed to grow up into young adulthood (45–60 days), and are tested for

grip strength, an adverse effect from prenatal exposure would be considered a developmental effect. Furthermore, if these animals were also tested for grip strength on day 300 (after sexual maturity), adverse effects would still be classified as Adevelopmental@ because exposure occurred *in utero.*

However, when considering continuous-exposure experiments (multi generation studies or when offspring are exposed postnatal after sexual maturity), Adevelopmental effects@ and Asystemic effects@ at the point of sexual maturity are categorized differently. Therefore, in a multi generation study, at the time when the F1 animals are mated to produce the next generation, the systemic category (or reproductive or neurological, etc.) is used.

Table 3-17. Developmental Effect Endpoints

Effect	Less serious	Serious
STRUCTURAL ABNORMALITY		
Delayed ossification	+	
Skeletal anomalies (Shina bifida, cleft palate, fused ribs, webbed feet)		+
Skeletal anomalies (ring tail[a], supernumerary ribs, wavy ribs)	+	
Visceral anomalies (heart defects)		+
Ultrastructural changes[b]	+	
ALTERED GROWTH		
Alteration in offspring organ weight[c]	+	
Alteration in offspring body weight[c]	+	
Changes in crown-rump length[c]	+	
FUNCTIONAL DEFICIENCY		
Immunosuppression in offspring		+
Systemic effects		+
Behavioral abnormalities (see Table 3-15a)		+

[a] Ringtail–a disease of obscure etiology in suckling rats in which one or more fine constricting ring occurs at some place along the length of the tail.

[b] Changes in cellular structure (cellular organelles).

[c] Could be considered serious, depending on the degree of severity.

Functional deficiency is defined as alterations or delays in functional competence of the organism or organ system following exposure to an agent during critical periods of development pre- and postnatal. Examples are:

- Immunosuppression (suppression of natural immune responses) in offspring. Immune dysfunction may lead to increased risk of infectious diseases or to development of neoplasia, autoimmune disorders, or allergies. Any of the immunological endpoints listed in Table 3-14 apply.

- Behavioral tests in offspring. Many of the neurological tests listed in Table 3-15a are used in studies of newborns to assess behavioral abnormalities in developing offspring. Measurement of the course of development of swimming behavior, for example, is a common technique for the evaluation of neuromotor development. The neuromotor system is the system commonly studied when functional development is being assessed. Evaluation of motor development must be of primary consideration in detecting toxicity because the performance of certain responses is known to be influenced by the testing conditions used and the motivational state of animals. To accurately assess the behavioral effects of any substance, a test battery must use multiple behavioral endpoints.

Maternal toxicity. ***Findings of developmental toxicity in the presence of maternal toxicity (i.e., when adverse developmental effects are produced only at maternally toxic doses) are still considered to represent developmental toxicity and should not be discounted as being secondary to maternal toxicity.*** Maternal toxicity (even in the absence of developmental toxicity) is an important endpoint to evaluate in the context of all available toxicity data. The following are some examples of maternal toxicity endpoints.

- Mortality.

- Gestation length (when allowed to deliver pups).

- Body weight.

- Body weight change.
- Organ weights (in cases of suspected organ toxicity and when supported by adverse histopathology findings).
- Food and water consumption (where relevant).
- Clinical evaluations, including types and incidence of clinical signs, enzyme markers, and clinical chemistries.
- Gross necropsy and histopathology.

Body weight and changes in body weight are viewed collectively as indicators of maternal toxicity for most species. These endpoints may not be as useful in rabbits, because body weight changes in rabbits are not good indicators of pregnancy status. Changes in maternal body weight corrected for gravid uterine weight at sacrifice may indicate whether the effect is primarily maternal or fetal. For example, there may be a significant reduction in weight gain and in gravid uterine weight throughout gestation but no change in corrected maternal weight gain, which would generally indicate an intrauterine effect. Conversely, a change in corrected weight gain and no change in gravid uterine weight generally suggest maternal toxicity and little or no intrauterine effect.

Because the maternal animal and not the conceptus is usually treated during gestation, developmental toxicity data may be presented as incidence per litter or as number and percent of litters with particular endpoints, as in the following examples.

- Litters with implants:

  Number of implantation sites/dam
  Number and percentage of live offspring/litter
  Number and percentage of resorption/litter
  Number and percentage of litters with resorption
  Number and percentage of late fetal deaths/litter
  Number and percentage of litters with nonlive (late fetal deaths + resorption) implants/litter
  Number and percentage of affected (nonlive + malformed) implants/litter
  Number and percentage of stillbirths/litter

- Litters with live offspring:

  Number and percentage of litters with live offspring
  Number and percentage of live offspring/litter
  Mean offspring body weight/litter
  Number and percentage of externally malformed offspring/litter
  Number and percentage of viscerally malformed offspring/litter
  Number and percentage of skeletally malformed offspring/litter
  Number and percentage of malformed offspring/litter
  Number and percentage of litters with malformed offspring
  Number and percentage of litters having offspring with variations
  Individual offspring and their malformations and variations (grouped according to litter and dose)
  Clinical signs (measured at intervals until study termination)
  Gross necropsy and histopathology

The following list of developmental toxicology references may be useful to chemical managers and principal authors. (Contractors are not required to purchase these publications.)

1. EPA. 1986. Guidelines for the health assessment of suspect developmental toxicant. Federal Register 51(185):34028.

2. EPA. 1989. Proposed amendments to the guidelines for the health assessment of suspect developmental toxicant. Federal Register 54(42):9386.

3. EPA. 1991. Final guidelines for developmental toxicity risk assessment. Federal Register 56(234):63798-63826.

4. Kimmel CA, Buelke J. 1981. Developmental toxicology. In: Dixon R, ed. Target organ toxicology series. New York, NY: Plenum Press, 233.

5. Rogers, JM, Kavlock, RJ. 1996. Developmental Toxicology. In: Klassen C, Amdur M, Doull J, eds. Toxicology: The basic science of poisons. 5th edition. New York, NY: McGraw Hill. 301-331.

Under developmental effects, there should be some discussion of whether effects were observed at levels that also caused maternal toxicity. Do not dismiss developmental effects in favor of maternal toxicity.

As stated above, reproductive effects that are also considered developmental should be mentioned under developmental effects as well, and they should be included in the LSE table with the other developmental effects.

Cancer

The cancer category consists of human and animal studies which consider tumor incidence as an endpoint. For epidemiological studies, the incidence of cancer effects should be provided wherever statistics are not reported and wherever incidence data can supplement information on the statistical significance of the results. NOAELs for cancer are not included, and cancer effects should always be categorized as "serious LOAELs" and CELs should be indicated where applicable.

When presenting EPA cancer-potency estimates in the text, be sure to include all caveats (e.g., the unit risk should not be used if the air concentration exceeds ___). All studies used in the cancer risk estimate should have been discussed in the text preceding the EPA estimates. If the EPA estimates involved extrapolation across routes of exposure, this information should be included and the justification for the cross-route extrapolation provided (e.g., health effects and toxicokinetic similarities).

3.3 GENOTOXICITY

Genotoxicity studies consist of *in vitro* and *in vivo* studies investigating the mutagenicity of the compound. Genotoxicity studies presented in this section should define the exposure conditions (level, duration, species, and strain) and effects observed. This section should be treated the same as the others, except more emphasis should be placed on describing the exposure conditions, because the genotoxicity studies are not presented in the tables and figures. Conclusions regarding the genotoxicity of the compound following the specified *route* of exposure should be made.

3.4 HEALTH EFFECTS IN WILDLIFE POTENTIALLY RELEVANT TO HUMAN HEALTH (*OPTIONAL)*

This section is optional depending on the substance that is being profiled. The decision to include a Wildlife section should be made after careful evaluation of the literature and discussion between the principal author and the chemical manager. This section should focus on available studies observed in wildlife that may be relevant to humans in terms of wildlife acting as possible sentinels for human health (NRC 1991). See Attachment K for an example of this section.

In the event that a Wildlife section (3.4) is developed, the sections of Chapter 3 that follow should be renumbered accordingly so that Toxicokinetics becomes section 3.5 and so forth.

3.4 TOXICOKINETICS

The discussion in this section is likely to overlap with Section 3.5 on Mechanisms of Action. Where necessary to provide a clear narrative, information in Section 3.5 should be referred to in this section (Toxicokinetics); however, as much as possible, any detailed discussion of mechanisms should occur only in Section 3.5.

This section, like all preceding sections, should provide a synthesis and weight-of-evidence analysis, with a description and discussion of key studies. In both the text and tables, special attention should be given to providing quantitative data such as the rate coefficients/constants for absorption, distribution, metabolism, excretion, and elimination. Metabolic parameters, such as the maximum velocity (V_{max}) and the Michaelis-Menten coefficient (K_m), for specific enzyme-catalyzed metabolic pathways are quite useful, because these may aid in the identification of dose-response thresholds. Attention should also be paid to changes in kinetic parameters with dose (e.g., transition from linear to nonlinear kinetics), which may be demonstrable only in studies in which pharmacokinetics have been studied over a sufficiently wide range of doses.

Presently, pharmacokinetic parameters are available for a limited number of chemicals. However, the literature should be searched for qualitative and quantitative data on biochemical (e.g., V_{MAX}, K_m) and physiological (e.g., blood:air and blood:tissue partition coefficients, cardiac output, body weight, blood flow rates, tissue volumes) parameters, as well as for data on the physical-chemical properties of the chemical, such as rate coefficients. Sex and species differences (especially between humans and animals) and route of administration differences (including those that may indicate a significant first-pass effect or enterohepatic recycling input) are also of importance here. Profiles should reflect how well authors have defined what they are measuring in kinetic studies. For example, when elimination is followed after administration of a radiolabeled chemical, assessing the researchers' methodology for separating the parent compound from its metabolites is essential. Total radioactivity measurements, while providing information on radiolabel retention, contribute little to the understanding of the relationships between dose, body burdens, elimination rates, and toxicodynamics, and should be used only with caution.

In recent years, especially for VOCs, physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling has been introduced to the risk assessment methodology. These models include both the kinetics and the dynamics of an administered dose. Such studies not only permit calculation of the "dose" of the administered compound or active metabolite(s) delivered to target organs, but also permit extrapolation of animal data to humans. In addition, PBPK/PD modeling studies may provide information on the mechanism of action. In Section 3.3.5 of the profile, information (in brief) should be presented on all available models, with more detailed discussion of the model(s) that best fits the existing data.

Overview. Several introductory paragraphs should be inserted under this heading (3.4 Toxicokinetics). These paragraphs should summarize the information in the four sections (absorption, distribution, metabolism, and elimination/excretion) and discuss the information available for the principal routes of exposure (inhalation, oral, and dermal). If there is evidence of dose-dependent kinetics, this should be discussed.

PBPK modeling data should be presented, together with any assumptions or known uncertainties and an explanation of whether or not the models were adequately validated.

The following sections discuss toxicokinetic data by major headings (absorption, distribution, metabolism, and elimination and excretion). Each section is organized by exposure pathways (inhalation, oral, and dermal). Exceptions are noted below. "Other Routes of Exposure" can be added as a subheading to the subsections. As in the discussion of toxicity, organize the discussions by human versus animal studies and, within these divisions, by duration of exposure where possible (especially for the duration of exposure in inhalation studies and the dose-time interval for repeated dosing/exposure studies).

3.4.1 Absorption

The discussion of absorption should explain the process by which the substance crosses biological membranes, and the site(s) of uptake where the substance enters the systemic circulation. (The reader should be referred to Section 3.5, Mechanisms of Action, for full discussion, where warranted.) Differentiate between exposure and dose. For example, specify administered dose, systemically absorbed dose, or target organ or tissue dose. Also, specify and distinguish between the rate and the extent of systemic absorption, especially "peak" values and steady-state concentrations. Focus on data that provide quantitative estimates of the amount absorbed and the absorption rate coefficient for each route of exposure. When known, give levels (percentages) of the substance absorbed following inhalation, oral, or dermal administration. Be particularly careful to mention the dosage vehicle for oral or dermal dosing, especially when more than one study is cited. Identify and discuss any other factors that are important determinants of absorption, such as changes in the rate and amount of absorption over a range of doses, effects due to chemical form or method of presentation (e.g., in water versus food), the nutritional status of the dosed animals, and so on.

Because some compounds may have only limited water solubility, and because the presence of food (especially fatty food) in the gastrointestinal tract may significantly affect the rate and extent of absorption of lipid-soluble environmental chemicals (often decreasing the rate but

increasing the extent), describe how the chemical was administered to test animals. Indicate whether this is likely to be the same mode of exposure in humans. An absorption rate or extent in an animal study in which the chemical was incorporated into the food may have little predictive value for the rate and extent of absorption of the chemical by humans from drinking water. If the mode of oral administration in the study is unclear, or if the general relevance of the animal study for likely routes of human exposure is unclear, state this in the text and identify the absence of reliable and relevant data as a data need. Overall, if reliable data are not available or are questionable, say so.

Guidance specific to children=s health

- Is absorption known or suspected to be different in children?

- Are there nutritional deficiencies that enhance the absorption of [Chemical X] in children or animal models (e.g., influence of calcium and iron deficiencies and fasting on absorption of lead)?

3.4.2 Distribution

The discussion of systemic distribution should include the extent (i.e., concentrations or amounts) of distribution to major organs and tissues. A comparison of concentrations or amounts of the chemical distributed to different tissues is more important than data for single tissues. If available, autopsy data should be presented in this section. If total radioactivity studies are included in the distribution section, caveats need to be included in the text that no distinction can be made between parent compound, metabolites, or "recycled" carbon incorporated into normal body macromolecules. Partition coefficients (blood:tissue) should be provided here, if known, as these are important parameters for PBPK modeling.

Focus on bioaccumulation in repetitive dosing studies; for example, describe data showing that repeated doses result in a steady state. The discussion should refer to any known mechanisms involved in the translocation of the substance(s) to tissues (e.g., passive diffusion, facilitated/active transport), including whether one or more depots for the sequestration of chemicals (e.g., the fat for lipophilic substances) are involved. (Refer the reader to Section 3.4 for full discussion, where warranted). If depots are involved, mention whether sequestered material is readily available for subsequent redistribution. State whether the parent compound or metabolites bind to plasma or tissue proteins. (Again, refer to Section 3.4 where warranted.) Does binding to plasma proteins restrict hepatic metabolism during a first pass or otherwise contribute to delivery-limited elimination by the liver or other organs? Are there differences in distribution and/or rate depending on the route of administration? Where data are available, bioaccumulation in target organs should be discussed.

Guidance specific to children's health

- Is distribution known or suspected to be different in children?

  - Are there nutritional deficiencies that change the distribution of [Chemical X] in children or animal models?

- Do [Chemical X] or its active metabolites reach (this may depend on the route of exposure to the mother: inhalation, oral, or dermal exposure) and cross the placenta or placental precursors? Do [Chemical X] or its metabolites preferentially accumulate on the fetal side of the placenta? If possible, indicate quantitatively how much of [Chemical X] crosses the placenta. Does the placenta itself trap and accumulate [Chemical X]? **If there are intraperitoneal (i.p.) or intravenous (i.v.) data about the permeability of the placenta, they should be discussed in AOther Routes of Exposure@ subsections with caveats about extrapolating to inhalation, oral, or dermal exposure of the mother.** Point out that human is unlikely to be exposed to [Chemical X] by i.p. or i.v. routes, but that any positive data show that

[Chemical X] could cross the placenta if exposure was great enough to achieve comparable maternal blood levels. Of course, negative i.v. data could be interpreted to mean that [Chemical X] (at least the parent compound) would be unlikely to cross the placenta regardless of the exposure circumstances. **[Note that the scientist selecting literature must acquire the data about i.p. and i.v. exposure and placental transfer.]**

It is particularly important to discuss access to the placenta in cases where the active form of [Chemical X] could not possibly reach the placenta. An example of this would be inhaled formaldehyde. Although formaldehyde itself can cross link DNA and protein, inhaled formaldehyde is converted to formic acid on the surface of the upper respiratory tract, and inhaled formaldehyde itself never reaches the systemic circulation. Thus, inhaled formaldehyde would never reach the placenta, and small amounts of formic acid in the maternal blood are likely to be innocuous.

- Can [Chemical X] or its metabolites reach (this may depend on the route of exposure to the mother: inhalation, oral, or dermal exposure) and get into breast milk? Are [Chemical X] or its metabolites preferentially accumulated in breast milk? If possible, indicate quantitatively how much of [Chemical X] is transferred to the breast milk. **If there are relevant intraperitoneal (i.p.) or intravenous (i.v.) data about transfer into breast milk, they should be discussed in AOther Routes of Exposure@ subsections with caveats about extrapolating to inhalation, oral, or dermal exposure of the mother.** Point out that humans are unlikely to be exposed to [Chemical X] by i.p. or i.v. routes, but that any positive data show that [Chemical X] could be transferred to breast milk if exposure was great enough to achieve comparable maternal blood levels. Of course, negative i.v. data could be interpreted to mean that [Chemical X]Cat least the parent compoundCwould be unlikely to transfer to breast milk regardless of the exposure circumstances. **[Note that the scientist selecting literature must acquire the data about i.p. and i.v. exposure and transfer into breast milk.]**

It is particularly important to discuss access to the breast milk in cases where the active form of [Chemical X] could not possibly reach the breast. An example of this would be inhaled formaldehyde. See the previous discussion about the placenta.

- Is [Chemical X] stored in maternal tissues *during pre-conception exposure*, and if so, can these stores be mobilized during pregnancy or lactation? Will this process result in exposure to the embryo/fetus or neonate?

- **Discuss the pharmacokinetic plausibility of the active form of [Chemical X] actually reaching parental germ cells. It is particularly important to discuss this issue in cases where the active form of [Chemical X] could not possibly reach the germ cells. An example of this would be inhaled formaldehyde. See the previous discussion about the placenta.**

  Remember that parental germ cells were formed when the parents themselves were in utero, so relevant exposure times could range from the parental gestation period to the time of conception. Damage to germ cells could either be genetic or, theoretically, epigenetic (e.g., changes in DNA methylation).

  This issue is particularly important if [Chemical X] has been shown to be genotoxic in test systems or if the results of any studies link preBconception exposure of either parent with germ line mutations, developmental defects, childhood cancer, or other health effects. If this is the case, crossBreferences should be made to the appropriate sections. If there are no data on the ability of [Chemical X] to reach the germ cells, say so.

3.4.3 Metabolism

The discussion of metabolism should include information on metabolic pathways (involving catabolic and anabolic reactions) that either convert the substance to a form that is less toxic

and/or can readily be excreted or that produces a biologically active intermediate that is responsible for the toxic action (i.e., metabolic activation). Discuss pathways of detoxification that are capacity limited. (Refer the reader to Section 3.4 for discussion of how capacity-limited pathways contribute to or cause toxicity.) Levels of the chemical producing such "saturation" should be discussed in this section if they are available in the literature.

This section should be organized by routes of administration, if route is not an important factor, an integrated discussion may be used. If specific organs or tissues are qualitatively or quantitatively involved, they should be mentioned and major or minor metabolic pathways should be described. *In vitro* studies may be important not only because they provide important information on intermediates and pathways but also because, for enzyme-catalyzed reactions, they allow the determination of V_{max} and K_m. Discuss qualitative and/or quantitative strain or species differences in metabolic pathways. Dose dependency is an important concept in discussions of physiological, metabolic, and toxicologic thresholds and should be stressed. Doses that cause one or more metabolic pathways to be "saturated" may be evaluated if these constants are known or if they are clearly identified by nonlinearity of the applied dose and evoked toxic response.

A diagram of the metabolic pathway should be included whenever there are adequate data (see Exhibit 15). The pathway(s) leading to the toxic metabolite(s) should be identified. Phase II metabolism often contributes to the generation of potentially reactive metabolites and/or provides a means of transport from the site of formation (e.g., the liver) to target tissues. Hence, phase II reactions should be included in the diagram as a rule and given equal consideration in the text unless it is well known that these pathways do not contribute to toxification/detoxification processes. If metabolism differs with the route of exposure, the diagram(s) should be labeled to reflect this. Enzyme systems involved in the metabolism of the substance should be indicated above the arrows. Major and minor pathways should be identified as such. The diagram should serve as an illustration for the text and not a replacement. Where relevant, activation and detoxification pathways, including those involving both phase I and phase II reactions, should be indicated.

Guidance specific to children=s health

- Is metabolism of [Chemical X] known or suspected to be different in children? If the enzymes that metabolize [Chemical X] are known, does their expression or activity differ in children in general? What is known about placental metabolism? Discuss relevant animal studies.

  See text and Table 2 [**Attachment L**] from Leeder and Kearns 1997 and text in *Pesticides in the Diets of Infants and Children* (NRC 1993) on developmental patterns of various enzymes. Alternative names for enzymes in **Attachment L** are provided in **Attachment M**. Note that in humans CYP2E1 expression begins several hours after birth and continues to increase during the first year of life (Vieira et al. 1996). The attached tables are intended only as an aid in outlining this section, and the information in them should only be a starting point in writing this section. New additions are made to the literature daily. If [Chemical X] is found to be metabolized by a certain enzyme, then a thorough literature search should be done on the enzyme and childBspecific search terms, and perhaps age. If a relevant enzyme is found to vary developmentally, then the original papers documenting this variation should be retrieved and referenced in the Toxicological Profile, and a copy of the papers should be submitted to the Division of Toxicology Child Health Coordinator.

- Are there nutritional deficiencies that change the metabolism of [Chemical X] in children or in animal models?

3.4.4 Elimination

Decay constants. In general, the following equation may be written for the excretion of a compound in the body: $C(t) = C(0) \times \{e^{-\alpha t} + e^{-\beta t} + e^{-\&t} + ...\}$ where C (t) is concentration at time t and C (0) is the initial concentration or concentration at time 0 in a given body compartment, usually the blood... α, β, &, etc. may be called decay constants; the equations are generally

written so that α>β>&>etc.; α is called the first order decay constant; β is called the second order decay constant; and & is called the third order decay constant. In general, the bigger the α, β, &, etc. constants are, the faster the compound disappears from the body, if the equation is describing excretion. A special case is when β = & = 0, then 0.693/α is called the half life or $t_{1/2}$ and in one half-life, the amount of compound present decays to half the original amount.

Elimination of a compound is usually described by the temporal relationship of blood concentrations postadministration. This process involves distribution, metabolism, and excretion of the compound. In the text, distinguish between excretion of the compound (i.e., removal from the body) and elimination (i.e., loss of the compound from systemic circulation). The kinetics may be of a simple first-order nature but more frequently require a multiexponential equation to describe them. Do not assume first-order half-life kinetics for persistent compounds. When available, the half-life of the substance in different tissues should be reported. Elimination also includes the half-life of the substance in different tissues. The terminal elimination rate is, perhaps, the most important parameter with respect to understanding the persistence of the substance in the systemic circulation. Initial elimination rates, observed following intravenous administration or after a peak blood concentration is reached following administration by other routes, are often useful indicators of rates of distribution.

The discussion of excretion should include quantitative data, where available, for the principal excretory routes: urine, feces (including biliary excretion), and exhaled breath. In a few cases, other elimination routes such as hair and nails, milk, sweat, and saliva may be operative, and therefore should be discussed. Specific routes of excretion may be included in PBPK models. Differences in excretion patterns between humans and animals, as well as between different species, strains, and sexes, should be discussed. The section should be specific for the exposure route where possible. For example,

3.4.1. Absorption
3.4.2. Distribution
3.4.3. Metabolism
3.4.4. Elimination

Guidance specific to children's health

- Is excretion known or suspected to be different in children?

  - Are there nutritional deficiencies that change the excretion of [Chemical X] in children or in animal models?

3.4.5 Use of PBPK/PD Models to Explain the Biological Basis for the Dose-Response Relationship

Begin this section with the following boilerplate.

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical substance that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a

species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically-sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-x shows a conceptualized representation of a PBPK model.

If PBPK models for [substance x] exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

(Insert figure of generic model structure.) (See exhibit 15.)

This section addresses the question, "Is PBPK/PD modeling for [substance x] possible?" The section should include basic pharmacokinetic studies, PBPK models, and biologically based dose-response (BBDR) models (i.e., toxicokinetic/pharmacodynamic models). The discussion of mathematical models should differentiate between broad-based models. Address the objectives and value of PBPK/PD models in species-to-species, high-to-low dose, and route-to-route extrapolations and in risk assessments for the profiled substance. Information (in brief) should be presented on all available models, with more detailed discussion of the model(s) that best fits the existing data. Discuss whether researchers have validated the models by comparing simulation with experimental data. If a PBPK model has not yet been developed and validated for a chemical, this should be stated in the text.

A summary table of model input data should be included when such data exist in sufficient detail to warrant a table. The table should also include physiological and anatomical parameters, e.g., tissue volumes; blood flow rates, cardiac output, and alveolar ventilation (see Andersen ME, Clewell HJ III, Gargas ML, Smith FA, and Reitz RH. 1987) physiologically based pharmacokinetics and risk assessment process for methylene chloride. Toxicol Appl Pharmacol 87:185-205). Provide an evaluation and assessment of the most appropriate values to use if many values exist for a given parameter. The rationale for selecting specific parameters must be provided in the text. Uncertainties in the interpretation of the pharmacokinetic and toxicological information considered for use in a PBPK/PD model should be outlined. A search of the literature should also include pharmacokinetics following intravenous administration, because this route avoids complications arising from interactions at the site of uptake and the sometimes complex factors involved in delivery of the dose to the systemic circulation (e.g., first-pass effect). Discuss whether the kinetic data suggest mechanistic considerations (such as capacity-

limited metabolic processes) for low-dose extrapolation applicable to the risk assessment process.

Guidance specific to children's health

- Are there PBPK models for children, fetuses/pregnant women, infants/lactating women, or humans at any other appropriate age? Discussion of general models for these stages may be appropriate.

3.5 MECHANISMS OF ACTION

The narrative for this section should present a brief overview of any known mechanisms of metabolism, absorption, distribution, and excretion, and then discuss any substance reactions or physiological processes that lead to or comprise the mechanism(s) of toxic effect. Keep in mind that one intent of this section is to provide a survey of places where clinical intervention can or might reduce the toxic effects of the profile substance, a subject that will be developed further in Section 3.11 (Methods for Reducing Toxic Effects). The parent compound, active metabolites, and any significant environmental breakdown products (identified in Chapter 7) should be discussed here.

If general information is known about the substance (i.e., chemical class, structural similarities, physical/chemical properties, etc.), the author should use reasonable conjecture to discuss a possible mechanism of action (based on the scientific literature) when conclusive evidence for a specific mechanism is not known. Potential areas of concern may be identified through structure-activity relationships.

Guidance specific to children=s health

- Is the mechanism of action known or suspected to be different in children? Discuss the evidence.

- Does [Chemical X] or its metabolites indirectly affect the fetus? Examples include interference with blood flow, oxygen, or nutrient transport to the placenta or with waste transport from the placenta.

- Does [Chemical X] or its metabolites indirectly affect the neonate during lactation?

3.5.1 Pharmacokinetic Mechanisms

The following topics should be addressed, but the underlined topics are not headings.

Absorption.

By what mechanism is the substance transferred from the gut, lungs, and skin to the blood (or site of toxic action, if the blood is not involved in transport)? For example, are the mechanisms passive or active? Is a specific facilitated or active transport mechanism involved? Does absorption involve an intermediary (e.g., metallothionein)? Is the absorption process saturable or capacity limited? Does the parent compound have the ability to ionize? If so, what section of the gastrointestinal tract is likely to absorb it, based on its pK_a? If the compound is lipophilic, is it of a small enough molecular weight to diffuse passively across the cell membranes of gut, dermal, or pulmonary epithelial cells? Can it be metabolized by either gut microflora or enzymes of the intestinal mucosa? If so, how does this affect absorption? Is it absorbed primarily into the lymphatics or the blood? Does diet or micronutrients affect absorption? Is information available on the influence of different vehicles or diluents on dermal or oral absorption? Is pulmonary absorption perfusion or ventilation limited?

Distribution

What is the pattern of tissue distribution of the substance and its metabolites? Is distribution dose-related? What is the mechanism by which the chemical is transported from the site of absorption to the site(s) of deposition? Is there an intermediary, such as a binding protein? Is there a first-pass effect in the liver, if the compound is absorbed from the gastrointestinal tract

into the blood? If the compound is volatile, is it blown off during first-pass pulmonary circulation?

Storage

Are there mechanisms for storage, e.g., binding to particular cellular macromolecules such as metallothionein, lipophilic partitioning into adipose tissue, or sequestration to "deep" depots such as bone?

Excretion

How is the chemical eliminated from the body? What contribution is made by excretion of the parent compound or metabolites via renal, pulmonary, biliary, and other routes? Are these excretion mechanisms active or passive? Do they show evidence of capacity limitation (saturation) within the dose range of animal testing and/or expected human exposure? In regard to metabolic elimination, is there a significant contribution by tissues other than the liver? If more than one pathway of metabolism is involved in the metabolic elimination of the compound, do the various pathways show differences in capacity limitation that might cause the metabolic profile of the substrate to change as a function of dose? Is there a "futile cycle" in the metabolism of the chemical? (An example is the N-acetylation of dapsone in humans; the N-acetyldapsone formed cannot be excreted into urine but must be first deacetylated back to dapsone before elimination can occur, either by urinary excretion of dapsone or metabolism to N-hydroxydapsone, which can be excreted.) Are there mechanisms for reabsorption, such as cleavage of conjugates in the urine or enterohepatic circulation?

Effect of Dose and Duration of Exposure on Toxicity

Is the dose-response curve unusually steep, or is there other reason to expect that toxicity seen at high doses may not extrapolate linearly to low doses? Is there reason to expect that capacity limitation of pathways of metabolism and/or excretion may influence dose-response relationships for toxicity? Can such phenomena indicate that a threshold in the dose-response relationship for toxicity is to be expected? Can toxicity be related to a specific concentration of chemical in a target organ? Is toxicity reversible and related to excretion of the chemical? Can the organism adapt to xenobiotic exposure, such as by induction of metabolic or DNA repair

enzymes? If there is any question about whether a particular endpoint represents an adaptive response, this is the appropriate place to discuss the issue. Is there evidence to suggest that chronic exposure may lead to depletion of essential cosubstrates for metabolic elimination such that dose-response relationships may change as a function of time of exposure? If so, is this likely to be different in situations of high- and low-dose exposure?

In cases where toxicity results from the action of toxic active/reactive metabolite(s) and where the toxicity assessment is based on epidemiological data gathered from occupational exposure, clearly state how the dose/exposure level was calculated and the confidence that can be placed in this assessment. Indicate whether or not the available evidence distinguishes between causality of the chronic low-level exposure and the possibility of occasional accidental higher level exposure. If appropriate, indicate PBPK data needs on the metabolic distribution of high versus low doses of the chemical.

Route Dependent Toxicity

Is toxicity route-dependent? If so, is there a pharmacokinetic explanation?

3.5.2 Mechanisms of Toxicity

Effects of Metabolism on Toxicity

Is toxicity associated with the parent chemical, its metabolite(s), or a combination(s) of parent compound and metabolites? Is there reason to believe that toxicity is initiated by the action of a chemically reactive metabolite of the parent compound and/or by reactive oxygen species generated by redox cycling of one or more of its metabolites? In what organs are these metabolic enzymes present? Do the pathways of metabolism become capacity limited or saturated within the dose ranges used in animal testing or in the expected range of human exposure? Discuss methods, if available, to identify the doses at which capacity limitation of pathways may influence dose-response relationships. Can the ratios of various metabolites or increases in the absolute levels of metabolites or of metabolite-derived products be used as biomarkers of effect and/or susceptibility? Which pathways have the lowest capacities, and can these capacities be related to possible exposure levels?

What is known about the relationships between target tissue dose and applied dose? In the case of toxicity resulting from an active or reactive metabolite, what information is available that relates production of the ultimate toxic metabolite to metabolic parameters and metabolic distribution to applied dose? Are ultimate toxic metabolites formed in the target tissue or transported there after formation elsewhere, either as such or as proximate metabolites? Can the rate of delivery of proximate or ultimate toxic metabolites to target tissues be estimated from PBPK models?

Do relevant human polymorphisms (e.g., allelic variation for key metabolic pathways) exist? If so, are they likely to influence susceptibility? (Polymorphisms usually have to be found by doing a search on the identified enzymes; such information is often not identified in a substance-specific search.) Discussion should be linked with both Section 3.10 (Populations That Are Unusually Susceptible) and Section 3.12 (Adequacy of the Database).

Target Organ Toxicity

What is currently known about the mechanism by which the chemical initiates organ toxicity? Present the evidence for individual steps in the toxic sequence, indicating what is established and what is hypothesized. (A diagram may be helpful here.) Indicate alternate hypotheses where there are adequate supportive data. Discussion should be linked to Section 3.12 (Adequacy of the Database).

Are there human diseases or metabolic conditions that predispose the target organ to damage? (This may require a separate search on target organ impairment.) Discussion should be linked to Section 3.10 (Populations That Are Unusually Susceptible).

Are there species and/or strain features or special metabolic conditions in the laboratory animals used in toxicity testing that may influence their responsiveness (due to enhanced or decreased susceptibility) as compared with humans? Are physiological or anatomical differences of concern in the extrapolation of the animal data to humans (i.e., likely to cause under- or overestimation of dose-response relationships)?

Carcinogenesis

Mechanisms for both non-cancer and cancer effects should be discussed. For cancer, the following issues should be addressed, if possible. Is this xenobiotic a complete carcinogen? An initiator? A promoter? Can DNA adducts be isolated? Have mutation spectra (a unique pattern of transitions, transversions, and basepair deletions or additions characteristic of exposure to a particular mutagen) been identified? Can electrophiles (potential DNA attackers) be identified in the metabolic scheme? If so, are these electrophiles explicitly identified on the metabolic diagram in Section 3.4.3 (Metabolism)? Is the xenobiotic an intercalator? A clastogen?

3.5.3 Animal-to-Human Extrapolations

Discuss qualitative and quantitative differences in the metabolic pathways for relevant comparison species (i.e., species for which the majority of the toxicity data are available, or from which key data are derived). Do these metabolic differences explain interspecies variance in toxicity? Are certain animal models inappropriate to use for extrapolation to humans?

If toxicity differs between species, what is the most appropriate animal model for human health effects? Is there a biologically plausible mechanism for explaining positive epidemiological studies? Have certain health effects been demonstrated in animal models that are unlikely to occur in humans (e.g., male rat-specific nephropathy caused by α_{2u}-globulin accumulation)? Does the mechanism suggest potential endpoints to examine in future epidemiological studies? Discuss relevant *in vitro* data and models.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Add section 3.6 - Toxicities Mediated Through the Neuroendocrine Axis immediately following section 3.5 - Mechanisms of Action. Continue to include "Endocrine Effects" under systemic effects in Chapter 3 (Health Effects).

Begin the section with the following boilerplate:

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992) and was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for A...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...@. To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning *endocrine disruptors.* In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as hormonally *active agents*. The terminology *endocrine modulators* have also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Mayr et al. 1992; Livingston 1978). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Hoel et al. 1992; Giwercman et al. 1993; Berger 1994).

Begin by discussing any pertinent (general or historical) review articles of endocrine disruption of [substance X]. Whether or not a generalized review is available will depend greatly on the availability of scientific information about the endocrine disrupting potential of [substance X] and other factors (i.e. public perception, widespread use of substance, etc.). Summarize literature pertaining to human health effects. Follow with discussion of endocrine disruption in laboratory animals, then in wildlife and fish. Data summarized should include the following information:

Females: disruption of normal sexual differentiation, ovarian function (i.e., follicular growth, ovulation, corpus luteum formation and maintenance), fertilization, implantation, and pregnancy. Also include relevant information on alterations of the uterus or endometrium (endometriosis) and mammary gland (breast cancer) as appropriate.

Males: disruption of normal sexual differentiation; testicular function (i.e., Leydig cell hyperplasia or tumors, Sertoli cell alterations/tumors, alterations in sperm production), and alterations of the prostate (prostatic hyperplasia/cancer).

Other endocrine organs: hypothalamus, pituitary, thyroid, parathyroid, adrenal, pancreas, paraganglia, and pineal body.

As a matter of science policy, the terminology "endocrine modulation" is not to be used in this section. This section addresses endocrine disruption and terminology should reflect the same. When no studies pertaining to endocrine disruption in humans or animals (laboratory or wildlife/fish) are located, the following boilerplate sentence should be inserted: **No studies were located regarding endocrine disruption in [humans and/or animals] after exposure to [substance x].** End by summarizing relevant *in vitro* studies. If no *in vitro* studies are located, insert the following boilerplate sentence: **No *in vitro* studies were located regarding endocrine disruption of [substance x].**

References:

-Adlercreutz H. 1995. Phytoestrogens: Epidemiology and a Possible Role in Cancer Protection. Environmental Health Perspectives, 101(5) 103-112

-Berger G. 1994. Epidemiology of Endometriosis. In: Modern Surgical Management of Endometriosis. Springer-Verlag, New York.

-US EPA. 1997. Special Report on Environmental Endocrine Disruption: An Effects Assessment and Analysis EPA/630/R-96/012

-Giwercman A, Carlsen E, Keiding N, and Skakkebake, NE. 1993. Evidence for increasing incidence of abnormalities of the human testis: A review. Environ Health Perspect 101 (Suppl1): 65-71

-Hoel DG, Davis DL, Miller AB, Sondik EJ, and Swerdlow AJ. 1992. Trends in cancer mortality in 15 industrialized countries, 1969-1986. J. Nat Cancer Inst 84:313-320

-Livingston, AL. 1978. Forage Plant Estrogens. J. Toxicol. Environ. Health 4: 301

-Mayer U, Butsch A and Schneider S. 1992. Validation of two in vitro test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. Toxicology 74: 135-149

3.7 CHILDREN'S SUSCEPTIBILITY

This section will immediately follow 3.6 - Toxicities Mediated through the Neuroendocrine Axis.

The following boilerplatewill be used to introduce this section.

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and in vitro models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children=s unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Widdowson and Dickerson 1964; Fomon et al. 1982; Owen and Brozek 1966; Altman and Dittmer 1974; Fomon 1966). The infant also has an immature bloodBbrain barrier (Adinolfi 1985; Johanson 1980) and probably an immature bloodBtestis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Leeder and Kearns 1997; Komori et al. 1990; Vieira et al. 1996; NRC 1993). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who

all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; West et al. 1948; NRC 1993). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility; whereas, others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

The full citations for the references mentioned in this boilerplate are listed in this guidance for

Chapter 9: References.

The scope of the Developmental Effects sections of the Toxicological Profiles has been broadened. In the past, the Developmental Effects sections of the profile covered only the interval from implantation through 18 years of age in humans and through sexual maturity in animals. The Reproductive Effects sections cover effects resulting from exposures during the interval from the generation of parental germ cells to conception up through implantation of the offspring. The scope of the Reproductive Effects sections has not changed. **The Developmental Effects sections will now include developmental health effects *on the offspring* resulting from exposures to *parental germ cells* (formed when the parents were in utero), *the conceptus through the preBimplantation blastocyst stage*, and all subsequent developmental stages up through 18 years of age in humans or sexual maturity in animals.** These Developmental Effects sections will discuss exposures that might result in developmental health effects *to the embryo or later stages of life*. Deaths at any stage before implantation will still only be discussed in the Reproductive sections because such outcomes do not affect the health of the embryo, fetus, infant, child, adolescent, adult, or adult's offspring. The reason for this change in scope is recent research in animals showing that exposure of parental germ cells or

preBimplantation conceptuses to certain mutagens can result in structural malformations in lateBstage fetuses and neonates, although these phenomena are often accompanied by an expectedly high death rate in litter mates (Rutledge et al. 1992; Spielmann and Vogel 1989; Rutledge 1997; Generoso et al. 1990). In theory, either genetic or nonBgenetic damage (such as changes in DNA methylation or disruption of the expression of key developmental regulatory molecules) to the parental germ cells or the preBimplantation conceptus could result in functional or structural defects in the offspring. Mutations and childhood cancer are also theoretical outcomes of preBimplantation damage. Organogenesis is still considered the most susceptible period for the induction of structural malformations.

References:

Rutledge JC, Generoso WM, Shourbaji A, Cain KT, Gans M, and Oliva J. 1992. Developmental anomalies derived from exposure of zygotes and firstBcleavage embryos to mutagens. Mutation Research 296:167–177.

Spielmann H and Vogel R. 1989. Unique role of studies on preBimplantation embryos to understand mechanisms of embryotoxicity in early pregnancy. Critical Reviews in Toxicology 20:51–64.

Rutledge JC. 1997. Developmental toxicity induced during early stages of mammalian embryogenesis. Mutation Research 396:113–127.

Generoso WM, Rutledge JC, and Aronson J. 1990. Developmental anomalies: mutational consequence of mouse zygote exposure. Banbury Report 34: Biology of Mammalian Germ Cell Mutagenesis, Cold Spring Harbor Press.

Authors of chapter 3 should be familiar with both a) the main literature search strategy and any supplemental search strategies used for [Chemical X] and b) whether these searches are likely to have missed any relevant resources. **Authors of chapter 3 are responsible for instigating supplemental literature searches [see Literature Search] as necessary.** The need for a supplemental literature search may become obvious at any time during Toxicological Profile development.

The following questions should be addressed **both** in the relevant sections of the Toxicological Profile (noted in **bold** in parentheses) and in this section. When necessary for clarity, define the specific stages of growth and development to which the discussion applies. **Section 3.7 is to be a STAND-ALONE section of the profile. Section 3.7 should be an ANALYTICAL SYNOPSIS of information discussed elsewhere in the profile, not a wordBforBword regurgitation of the information discussed in other sections.** Within each topic, please discuss human data first, then relevant animal data.

- *Must* be discussed, if only to say that no information is available.

- Should not be discussed if there is no relevant information.

- What health effects have been observed in children? [Example: childhood asthma discussed in the Respiratory Effects sections.] Are there health effects observed in adults that are also of potential concern in children? What health effects have been observed in adults exposed as children? What health effects have been observed in immature animals from embryos up through maturity? Do children and immature animals exhibit the same types of health effects as adults? Do the doses that cause effects in children and adults or in immature and adult animals consistently differ? How? Consider any epidemiologic studies that focus on the consequences of exposures before age 18 years, even if the effects are not evident until adulthood. If there are little or no data on children, state that "The effects of [Chemical X] have not been (thoroughly?) studied in children, but they would likely experience the same health effects seen in adults exposed to [Chemical X]." (**3.2 Discussion of Health Effects by Route of Exposure** and **2.0 Relevance to Public Health** if appropriate).

- Does the susceptibility of children to the health effects from [Chemical X] differ from that of adults? How? Why? Are there any specific theoretical reasons for thinking that embryos, fetuses, infants, children, and adolescents would differ from adults in their vulnerability? Such reasons might include whether the metabolic enzymes

activating or detoxifying [Chemical X] have age-dependent expression. Note that if children are less susceptible, or have the same susceptibility as that of adults, this fact should be stated and the evidence discussed. Relevant animal models should also be discussed. (**3.10 Populations That Are Unusually Susceptible**)

- Is the developmental process altered by the toxicant? Discuss data on children, animals, and in vitro developmental models. Remember that the reproductive, immune, and nervous systems especially continue to develop after birth. Developmental problems may include functional neurological development, such as learning deficits and deficits in social behavior. Consider endocrine disruption of developmental processes and any epidemiologic studies that focus on the consequences of exposures before age 18 years, even if the effects are not evident until adulthood. If the developmental process is altered by the toxicant, how does the effective dose or range of effective doses in children compare with that in adults? If developmental effects only occur near maternally toxic doses, this point should be discussed. (**3.2 Discussion of Health Effects by Route of Exposure** and in **2.0 Relevance to Public Health** if appropriate).

- Do [Chemical X] or its active metabolites reach (this may depend on the route of exposure to the mother: inhalation, oral, or dermal exposure) and cross the placenta or placental precursors? Does [Chemical X] or its metabolites preferentially accumulate on the fetal side of the placenta? If possible, indicate quantitatively how much of [Chemical X] crosses the placenta. Does the placenta itself trap and accumulate [Chemical X]? **If there are intraperitoneal (i.p.) or intravenous (i.v.) data about the permeability of the placenta, they should be discussed with caveats about extrapolating to inhalation, oral, or dermal exposure of the mother.** Point out that humans are unlikely to be exposed to [Chemical X] by i.p. or i.v. routes, but that any positive data show that [Chemical X] could cross the placenta if exposure was great enough to achieve comparable maternal blood levels. Of course, negative data could be interpreted to mean that [Chemical X]Cat least the parent compoundCwould be unlikely to cross the placenta regardless of the exposure

circumstances. **[Note that the scientist selecting literature must acquire the data about i.p. and i.v. exposure and placental transfer.]**

It is particularly important to discuss access to the placenta in cases where the active form of [Chemical X] could not possibly reach the placenta. An example of this would be inhaled formaldehyde. Although formaldehyde itself can cross link DNA and protein, inhaled formaldehyde is converted to formic acid on the surface of the upper respiratory tract, and inhaled formaldehyde itself never reaches the systemic circulation. Thus, inhaled formaldehyde would never reach the placenta, and small amounts of formic acid in the maternal blood are likely to be innocuous. (**3.4 Toxicokinetics**)

- Can [Chemical X] or its metabolites reach (this may depend on the route of exposure to the mother: inhalation, oral, or dermal exposure) and get into breast milk? Are [Chemical X] or its metabolites preferentially accumulated in breast milk? If possible, indicate quantitatively how much of [Chemical X] is transferred to the breast milk. **If there are intraperitoneal (i.p.) or intravenous (i.v.) data about transfer into breast milk, they should be discussed with caveats about extrapolating to inhalation, oral, or dermal exposure of the mother.** Point out that humans are unlikely to be exposed to [Chemical X] by i.p. or i.v. routes, but that any positive data show that [Chemical X] could be transferred to breast milk if exposure was great enough to achieve comparable maternal blood levels. Of course, negative i.v. data could be interpreted to mean that [Chemical X] (at least the parent compound) would be unlikely to transfer to breast milk regardless of the exposure circumstances. **[Note that the scientist selecting literature must acquire the data about i.p. and i.v. exposure and transfer into breast milk.]**

It is particularly important to discuss access to the breast milk in cases where the active form of [Chemical X] could not possibly reach the breast. An example of this would be inhaled formaldehyde. See the previous discussion about the placenta. (**3.4 Toxicokinetics**)

- Is [Chemical X] stored in maternal tissues *during pre-conception exposure*, and if so, can these stores be mobilized during pregnancy or lactation? Will this process result in exposure to the embryo/fetus or neonate? (**3.4 Toxicokinetics**)

- **Does [Chemical X] or its metabolites indirectly affect the fetus? Examples include interference with blood flow, oxygen, or nutrient transport to the placenta or with waste transport from the placenta. (3.5 Mechanisms of Action)**

- **Does [Chemical X] or its metabolites indirectly affect the neonate during lactation? (3.5 Mechanisms of Action)**

- **Are pharmacokinetics known or suspected to be different in children? Are there nutritional deficiencies that change the pharmacokinetics of [Chemical X] in children or animal models (e.g., influence of calcium and iron deficiencies and fasting on absorption of lead)? (3.5 Toxicokinetics)**

- **Is metabolism of [Chemical X] known or suspected to be different in children? If the enzymes that metabolize [Chemical X] are known, does their expression or activity differ in children in general? What is known about placental metabolism? Are there nutritional deficiencies that change the metabolism of [Chemical X] in children or in animal models? Discuss relevant animal studies.**

See text and Table 2 [Attachment K] from Leeder and Kearns 1997 and text in National Research Council (NRC 1993) on developmental patterns of various enzymes. Alternative names for enzymes in Attachment K are provided in Attachment L. Note that in humans CYP2E1 expression begins several hours after birth and continues to increase during the first year of life (Vieira et al. 1996). The attached tables are intended only as an aid in outlining this section, and the information in them should only be a starting point in writing this section. New additions are made to the literature daily. If [Chemical X] is found to be metabolized by a certain enzyme, then a

thorough literature search should be done on the enzyme and childBspecific search terms, and perhaps age. If a relevant enzyme is found to vary developmentally, then the original papers documenting this variation should be retrieved and referenced in the Toxicological Profile, and a copy of the papers should be submitted to the Division of Toxicology and Environmental Medicine Child Health Coordinator. (**3.4 Toxicokinetics**)

- Are there PBPK models for children, fetuses/pregnant women, infants/lactating women, or humans at any other appropriate age? Discussion of general models for these stages may be appropriate. (**3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models.**

o Is the mechanism of action known or suspected to be different in children? Discuss the evidence. (**3.5 Mechanisms of Action**)

o Can parental exposure affect children (i.e., are there any transgenerational effects)? How? Remember that parental germ cells were formed when the parents themselves were in utero, so relevant exposure times could range from the parental gestation period to the time of conception. Damage to germ cells could either be genetic or, theoretically, epigenetic (e.g., changes in DNA methylation). Are there any studies linking preBconception exposure of either parent to germ line mutations, developmental defects, childhood cancer, or other health effects? Is [Chemical X] known to be genotoxic in test systems? Discuss the pharmacokinetic plausibility of the active form of [Chemical X] actually reaching the germ cells. It is particularly important to discuss this issue in cases where the active form of [Chemical X] could not possibly reach the germ cells. An example of this would be inhaled formaldehyde. If there are no data on the ability of [Chemical X] to reach the germ cells, say so. (**3.2 Discussion of Health Effects by Route of Exposure**, 3.4 **Toxicokinetics, and 3.3 Genotoxicity subsection**)

- Discuss any issues related to childhood cancer and either prenatal or postnatal exposures to [Chemical X]. (**3.2 Discussion of Health Effects by Route of Exposure**)

- Have any biomarkers of exposure or effect been validated in children or adults who were exposed to [Chemical X] during childhood? Are there any biomarkers of exposure or effect that are unique to children? Are there biomarkers in adults that identify previous childhood exposure? (**3.8 Biomarkers of Exposure and Effect**)

- Have any interactions with other chemicals been observed in children? Are there any interactions with other chemicals that are unique to children? Are interactions observed in adults likely to occur in children? (**3.9 Interactions with Other Chemicals**)

- Are there any pediatricBspecific methods for reducing peak absorption after exposure, reducing body burden, or interfering with the mechanism of action for toxic effects? Are any of the methods for adults contraindicated in children? Have the methods used in adults been validated in children? (**3.11 Methods for Reducing Toxic Effects**)

Appropriate care should be used in extrapolating from juvenile and newborn animals to humans (see pages 25 and 51 of NRC 1993):

> "For example, the newborn mouse or rat more nearly resembles the human fetus in the third trimester of gestation than the human infant at birth. On the other hand, the rate of maturation and growth of the mouse or rat after birth is relatively more rapid than the human. Thus, crossBspecies comparisons of potential toxicity for pesticides [or other chemicals] in the very young animal, although helpful, cannot be used in the same manner that crossBspecies comparisons are used with adult animals because of differences in developmental patterns...."

"Newborn mice and rats are among the most immature of commonly used test species, so it is not surprising that they often differ markedly from adult animals in sensitivity to chemicals.... Maturation in rodents is very rapid, so that even a few days of age can result in a marked disparity in test results...."

See **Attachment I: Age at weaning and sexual maturity for common laboratory species and humans** for assistance with interpreting the literature and knowing to which ages of humans the results of animal studies may apply.

When there is information on the class of compounds (such as organophosphates) in which [Chemical X] is included, it may be appropriate to discuss these data and state that "...extrapolating to [Chemical X] would suggest the following...." **It may be necessary to do a limited search on the class of compounds and childBhealthBspecific terms to see if such data exist.**

Authors of chapter 3 should be familiar with *Pesticides in the Diets of Infants and Children* (NRC 1993). Authors should *frequently consult this comprehensive review* as they write the child health sections.

The author who prepares section 3.7 will need to provide assistance to the author of **6.6 Exposures of Children**. The two authors should coordinate with each other on every draft. The author of section 3.7 will also be a primary contributor to **1.6 How Can [Chemical X] Affect Children?** And **1.7 How Can Families Reduce the Risk of Exposure to [Chemical X]?** And should collaborate closely with the other authors of these sections.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Begin this section with the following boilerplate.

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to [substance x] are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment

(e.g., DNA adducts). Biomarkers of effects caused by [substance x] are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, "Populations That Are Unusually Susceptible."

The author of Section 3.8 must link discussion of this section to other parts of the profile. Sections 1.8 (Is There a Medical Test to Determine Whether I Have Been Exposed to [Substance X]), 3.12.2 (Identification of Data Needs), 7.1 (Biological Samples), and 7.3.1 (Identification of Data Needs) specifically refer to biomarkers and should be entirely consistent with information discussed in Section 3.8. In addition, Sections 3.2 (Discussion of Health Effects by Route of Exposure) and 3.4 (Toxicokinetics) should be carefully reviewed and referenced within Sections 3.8.1 and 3.8.2.

Chapter 1 of *Biological Markers in Reproductive Toxicology* (NAS/NRC 1989) provides a good general discussion of this topic. A copy of this reference is being provided to each contractor.

Guidance specific to children's health

- *Must* be discussed, if only to say that no information is available.
- Should not be discussed if there is no relevant information.

- Have any biomarkers of exposure or effect been validated in children or adults who were exposed to [Chemical X] during childhood? Are there any biomarkers of exposure or effect that are unique to children? Are there biomarkers in adults that identify previous childhood exposure?

3.8.1 Biomarkers Used To Identify or Quantify Exposure to [Substance X]

This section should contain information that will help the reader identify biomarkers that can be used to determine whether or not exposure to the substance has occurred. These biomarkers do not necessarily need to be unique for exposure to the substance. Biomarkers discussed in this section can be those that are "shared" by other substances (e.g., phenols are "shared" biomarkers of exposure to benzene, lindane, dichlorophenols, and other aromatic compounds). Biomarkers of exposure can include the substance itself, a metabolite, and/or effects (effects can be singular or multiple). For example, inhibited serum cholinesterase activity is a biomarker of exposure and effect for organophosphate and carbamate pesticides.

The profiled substance or any known metabolite(s) that can be measured is considered a primary biomarker of exposure. As such, data on the excretion of the substance or its metabolites should be one of the first places to look for potential biomarkers. Indicate when the measured substance is not specific for exposure to one substance (e.g., urinary phenol can result from benzene or phenol exposure). Indicate substance or class confounders or other factors that might influence interpretation of the observed results, such as biological half-life and sequestering (e.g., in bone or fat).

When background levels of a biomarker are known to exist in human tissue or fluid (e.g., for essential mineral nutrients or for phenols or other compounds that might occur in the body through means other than exposure to the substance), state the normal ranges for that biomarker. Also state whether or not the levels of such biomarkers could rise significantly above their normal ranges due to exposures that might be expected to occur. Refer readers to Section 3.4 (Toxicokinetics).

Indicate effect biomarkers (i.e., cholinesterase activity) or panels of biomarkers (e.g., FEP levels, accumulation of Zn protoporphyrin and anemia) that can implicate exposure to the substance or its class. Focus on quantifiable cellular changes such as DNA adducts and enzyme levels. Nonspecific symptoms of exposure such as headache, tremor, and cough should generally not be discussed in this section. However, any symptom or combination of symptoms that are specific

for the substance or its class should be discussed (e.g., the combination of constriction of the pupils of the eyes and tremor are indicators of exposure to anticholinesterases).

State the dose or dose range at which these biomarkers of effect are expected to appear in humans, if known. Discuss interpretation of these biomarkers for identifying and/or quantifying exposure to the substance. Also discuss limitations and confounders associated with the use of a battery of biomarkers as indicators of exposure (e.g., other substances that can cause the same physiological effects). Check to see if there is an ACGIH Biological Exposure Index (BEI) for the chemical.

3.8.2 Biomarkers Used To Characterize Effects Caused by [Substance X]

Indicate the most sensitive organs and/or tissues. Focus first on biomarkers of effects, such as DNA adducts, enzyme levels, damaged or dead cells, and organ dysfunction that have been used in studies involving the profiled substance. These biomarkers may or may not be symptoms of exposure that are specific to the substance. Discuss interpretation of these biomarkers for characterizing effects caused by the substance. Also discuss limitations and confounders associated with relating biomarkers of effects to exposure to this substance, and indicate that other substances can cause the same effects as those caused by the profiled substance.

Additional biomarkers of effects caused by the profiled substance may exist but might not have been located during the substance-specific literature review. Do not discuss these additional biomarkers, but refer the reader to appropriate sources that cover biomarkers of the appropriate organ system(s). ATSDR has developed reports that cover biomarkers for effects on the immune, renal, hepatic (e.g., ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage 1990) and neurological (for example: OTA. 1990. Neurotoxicity: Identifying and controlling poisons of the nervous system. Washington, DC: U.S. Congress Office of Technology Assessment, U.S. Government Printing Office) systems. ATSDR will provide complete references for these reports. Also, refer the reader to Section 3.2 for a more detailed discussion of the effects caused by the profiled substance.

3.9 INTERACTIONS WITH OTHER SUBSTANCES

Discuss mechanism of the interaction, if known. Discuss the influence of other substances on the toxicity of the profile substance. Other substances should include pharmaceuticals, hazardous substances, and substances not designated as hazardous substances. As discussed in Section 3.2, limitations of all studies should be addressed, and studies in humans should be discussed before studies in animals. If interactions have only been demonstrated in animals or *in vivo*, speculate about whether such an interaction is likely to occur in humans, and give the basis for that speculation. Discuss effects that are potentiative, synergistic, antagonistic, inhibitory, or masking (see below). Also discuss the relative timing of the exposures producing the interaction (i.e., whether the interaction only occurs with simultaneous exposures or when one chemical precedes the other). Discuss the mechanism of the interaction, if known. Several types of interactions may occur. For example:

- Compounds may directly interact with one another, causing a chemical change in one or more of the compounds.
- One compound may affect the pharmacokinetics/metabolism of another such that the quantity of the biologically active moiety reaching the target organ is altered.
- One compound may modify the biological actions of the second by exerting biological effects that enhance or counteract the actions of the second compound
- A compound may cause alterations in the target or receptor(s) for the second compound.

Guidance specific to children's health

- Have any interactions with other chemicals been observed in children? Are there any interactions with other chemicals that are unique to children? Are interactions observed in adults likely to occur in children?

Definitions for Interactions

The definitions presented in the table below are oriented toward their use in risk assessment. For example the definition of a mixture actually describes mixed exposures. From a toxicologic standpoint, however, the joint exposures are similar to the single exposure (perhaps time-varying) that would result if the chemicals were physically combined into a true chemical mixture. The following definitions are generally consistent with those found in the literature.

Table 3-18. Definitions of Terms Used To Characterize Mixtures and Interactions

Term	Definition
Mixture	Any set of two or more chemical substances, regardless of their sources, that may jointly contribute to toxicity in the target population.
Simple mixture	A mixture containing two or more identifiable components, but few enough that the mixture toxicity can be adequately characterized by a combination of the component toxicities.
Complex mixture	A mixture containing so many components that any estimation of its toxicity based on its component toxicities contains too much uncertainty and error to be useful. The chemical composition may vary unpredictably over time or with different conditions under which the mixture is produced. Complex mixture components may be generated simultaneously as by-products from a single source or process, may be intentionally produced commercial products, or may coexist because of disposal practices. Risk assessments of complex mixtures are preferably based on toxicity and exposure data for the complete mixture. Gasoline is an example.
Similar mixtures	Mixtures having the same components in slightly different ratios or having most components in nearly the same ratios with only a few different (more or fewer) components and displaying similar types and degrees of toxicity. Diesel exhausts from different engines are an example of similar mixtures.
Interaction	The circumstance in which exposure to two or more chemicals results in a qualitatively or quantitatively altered biological response relative to that predicted from the additive actions of the components administered

Term	Definition
	separately. The multiple chemical exposures may be simultaneous or sequential in time, and the altered response may be greater or smaller in magnitude (adapted from NRC 1980). For quantitative evaluations, the "no-interaction" prediction is based on dose or response addition, as appropriate.
Synergism	A response to a mixture of toxic chemicals that is greater than that suggested by the component toxicities.
Antagonism	A response to a mixture of toxic chemicals that is less than that suggested by the component toxicities.
Potentiation	A special case of synergism in which a substance that does not have a toxic effect on a certain organ or system on its own increases another chemical's toxicity when added to it.
Inhibition	A special case of antagonism in which a substance that does not have a toxic effect on a certain organ or system on its own lessens another chemical's toxicity when added to it.
Masking	A situation in which the toxic effect of one chemical is not displayed because of functionally competing effects from another chemical. The most striking example is when the carcinogenic activity of a mixture is not observed at experimental doses because of more obvious toxic signs, particularly mortality, induced by other toxic components.

Source: EPA. 1988. Technical support document on risk assessment of chemical mixtures. EPA/600/8-90/064, 1-8 to 1-10
NRC 1988

Table 3-19. Selected Examples of Types of Interactions Between Toxic Compounds

Pair of toxic, genotoxic exposures	Kind of interaction	Effect
Benzene + radiation	Additive or synergistic	Leukemia
Cigarette smoking + β-naphthylamine	Additive or synergistic	Bladder cancer
Benzene + toluene	Antagonistic	Chromosomal damage
Carbon tetrachloride + ethyl or isopropyl alcohol	Synergistic	Hepatic and renal damage*

Carbon monoxide + methylene chloride	Synergistic	Cardiac damage*
Cigarette smoking + asbestos	Synergistic	Lung cancer*
Cigarette smoking + carbon monoxide	Synergistic	Cardiac damage*
Cigarette smoking + uranium (radon)	Synergistic	Lung cancer*
Sulfur oxides + air particulate	Synergistic	Chronic obstructive pulmonary disease*

*Indicates interaction is well established

Source: Trieff NM, Weller SC, Ramanujam S, Legator MS. 1990. Prediction of toxicological interactions in a binary mixture by using pattern recognition techniques: Proposed approach with a developed model. Teratogenesis Carcinog Mutagen 10:165-175.

See also: Krishnan K, Brodeur J. 1991. Toxicological consequences of combined exposure to environmental chemicals. Arc Complex Environ Studies 3:1-104.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section begins with the following boilerplate.

> **A susceptible population will exhibit a different or enhanced response to [substance x] than will most persons exposed to the same level of [substance x] in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of [substance x], or compromised function of organs affected by [substance x]. Populations who are at greater risk due to their unusually high exposure to [substance x] are discussed in Section 6.7, Populations with Potentially High Exposures.**

If there is evidence of a particularly susceptible population identified in the boilerplate, this evidence should also be specifically presented in the text of the profile.

Identify known or potential unusually susceptible populations. There may be some overlap between this section and Section 3.9 (Interactions with Other Chemicals). The text in this

section should be written from the perspective of a senior scientist discussing individuals who are likely to be more severely affected than the "average" individual by exposure to the profile substance. The text should discuss all reported and all potential susceptible populations. Do not rely solely on published reports of susceptible individuals specifically linked to the profiled substance (as has been the practice in previous profiles). Rather, start from the known toxicokinetics of the profiled substance, present reasonable conjecture concerning individuals that are likely to be more sensitive, and support the conjecture with cited literature where possible. The literature supporting such conjecture may, for example, come from standard literature concerning toxicokinetics, specific studies of the profiled substance, or studies of similar substances.

Some examples of populations to consider are:

- Individuals in who target organs of the profiled substance are already compromised or damaged; for example, individuals with certain types of anemia should be considered when discussing sodium nitrite, which can cause methemoglobinemia. Other possible compromised populations include individuals with impaired pulmonary function (e.g., due to asthma, emphysema, bronchitis, cystic fibrosis), cardiovascular function (e.g., due to angina, congestive heart failure, cardiomyopathy), impaired kidney or liver function, immune problems (human immunodeficiency virus infection), and hypertension.

- Individuals who are likely to be exposed to a substance that is known to interact adversely with the profiled substance, for example, alcoholics and carbon tetrachloride exposure. (Interactions between alcohol and carbon tetrachloride potentiates liver and kidney damage.)

- Populations known to be susceptible to a closely related substance or its class.

- The fetus or neonate, especially for substances that are known to cause developmental effects. Neonates or young children are generally more susceptible than older children. The organ systems that are immature during the first few months of life (e.g., the nervous, endocrine, reproductive, immune systems; teeth) are most susceptible to injury by chemicals.

- The elderly.

Although children and the elderly are frequently listed as populations at greater risk of chemical injury, both age groups may be more *or* less susceptible than the general population.

Note: Do not identify populations who are at risk because of unusually high exposure. (This is covered in Section 6.7.)

Guidance specific to children's health

- *Must* be discussed, if only to say that no information is available.
- Should not be discussed if there is no relevant information.

When updating Toxicological Profiles, authors should beware of preexisting text stating that children are more vulnerable based on review articles or speculation. Statements about susceptibility should be based on scientific evidence as discussed in Section 3.7 Children's Susceptibility. Authors need to actively check for consistency between this section and 3.7. Where appropriate, material from this section may be added to 3.7.

- Does the susceptibility of children to the health effects from [Chemical X] differ from that of adults? How? Why? Are there any specific theoretical reasons for thinking that embryos, fetuses, infants, children, and adolescents would differ in their vulnerability from adults? Such reasons might include whether the metabolic enzymes activating or detoxifying [Chemical X] have age-dependent expression. Note that if children are less susceptible, or have the same susceptibility as that of adults, this fact should be stated and the evidence discussed. Relevant animal models should also be discussed.

At the appropriate place in this section, the following boilerplate should appear:
"**A more detailed discussion of children's susceptibility can be found in Section 3.7.**"

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section begins with the following boilerplate:

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to [substance x]. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to [substance x]. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to [substance x]: [provide full citations of at least three readily available texts that specifically discuss the medical management of exposure to the profile substance] as follows:

Ellenhorn, MJ and Barcelous, DG, (eds.) 1988. Medical Toxicology: Diagnosis and Treatment of Human Poisoning. Elsevier Publishing. NY. Pp. 972-974.

Do *not* to use phrases such as "it is recommended," "the victim can be," "the victim should drink," "should be removed," "may be flushed," and so on. Instead, use language such as "has been suggested" or "common treatments include." In other words, the text should not appear to endorse any particular method of treatment, nor should a reader be able to use the text as a guide to treatment. Therefore, units of measure should be avoided. The text should be a "profile" of the existing information, not a guide to treatment or a reiteration of information contained in emergency treatment texts. Adverse effects of treatments should be discussed as appropriate.

Guidance specific to children's health

- Are there any pediatricBspecific methods for reducing peak absorption after exposure, reducing body burden, or interfering with the mechanism of action for toxic effects? Are any of the methods for adults contraindicated in children? Have the methods used in adults been validated in children?

3.11.1 Reducing Peak Absorption Following Exposure

This section should present a general overview of initial exposure management and treatment methods applicable to the compound, the intent of which is to reduce peak absorption (e.g.,

dilute with milk, then pump stomach; administer activated charcoal orally; wash skin and eyes; remove clothing). Again, the intent is to profile existing methods, not provide a guide to treatment. Therefore, avoid providing units of measure.

If one route of exposure is more important than others, this should be discussed. Also discuss known contraindications for any particular method that might be used (e.g., ipecac administration and emesis may be contraindicated for ingested caustics and hydrocarbons; water/milk should *not* be used under some circumstances).

3.11.2 Reducing Body Burden

This section presents and discusses methods for enhancing elimination of the absorbed dose or body burden, or for removing a persisting metabolite or by-product of the profiled substance from the body. Examples of treatments that belong in this section are chelation or dialysis therapy to remove metals, reduction of methemoglobin with methylene blue after nitrite exposure, use of specific antidotes against cyanide*, and use of activated charcoal to decrease enterohepatic circulation.

The section should begin with a brief discussion of the retention of the compound or its metabolites in humans, then:

- If the compound is retained by the body, if it can exert a toxic effect during its retention or release from storage (over any clinically relevant period or during certain physiologic states such as fasting or pregnancy), and if there are methods of reducing the burden, then discuss those methods.

- If the compound or its metabolites are not retained by the body or are not toxic while retained or when released from storage, then state this fact.

- If there are no known methods for reducing the body burden, then speculate about methods that might be developed. Speculation could be based on what is done with similar

*Such as inducing formation of methemoglobin for cyanide to bind to, or infusing thiosulfate to transform it to thiocyanate.

compounds or on knowledge of the organ system or the way the substance is released from storage.

- If a body burden reduction method is not commonly used, then discuss why it is not (e.g., because it is too expensive, not safe, not FDA approved).

3.11.3 Interfering With the Mechanism of Action for Toxic Effects

This section discusses clinical or experimental methods that can block the mechanism of toxic action at any point, from initial interaction of the substance with biochemical or physiological processes of the body to the actual physical damage or functional change. Examples of this are blocking conversion of 2-hexanone to 2, 5-hexanedione, using ethanol to reduce glycol or methanol metabolism, or using receptor blockers.

The section should address the following questions and discussion points.

- If the mechanism of action is not known, speculate on possible mechanisms of action based on the existing evidence discussion in the scientific literature, or structure-activity relationships (SAR). Then discuss possible methods for interfering with those mechanisms of action.

- If the mechanism is known but there are no known methods to interfere with that mechanism, then speculate on methods that might be worth researching, based on discussion in the scientific literature or knowledge about the mechanism or similar mechanisms.

- If the mechanism of action is known and a method for interfering with that mechanism is known but not widely used, then discuss the method's advantages and disadvantages and speculate on the potential for using the method to mitigate effects of exposure at NPL sites.

- If the mechanism of action is known and a method for interfering with that mechanism is known and widely used, then discuss the method and speculate on the potential for improving or increasing its use at NPL sites.

3.11 ADEQUACY OF THE DATABASE

This section begins with the following boilerplate.

> **Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of [substance x] is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of [substance x].**
>
> **The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.**

"NTP" should be used the second and third time the boilerplate is included in the profile. It is only necessary to define NTP when first used in the profile.

This section is divided into three subsections, as follows:

3.12.1 Existing Information on Health Effects of [Substance X]
3.12.2 Identification of Data Needs
3.11.3 Ongoing Studies

3.12.1 Existing Information on Health Effects of [Substance X]

Use the dot-matrix figure format (Exhibit 17) to illustrate both the positive and negative data that exist; prepare separate figures if there are significant differences in the toxicity of various congeners, isomers, or valency states of the compound.

A dot should be used whenever there is at least one report that provides information on the data box in question. The dot does not imply that the studies are adequate to draw firm conclusions about the effect; the dot only implies that at least one report has been located. The following boilerplate should be used.

> **The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to [substance x] are summarized in Figure 3-___. The purpose of this figure is to illustrate the existing information concerning the health effects of [substance x]. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.**

The text should also discuss the highlights of the figure, covering the human and animal figures, in that order. Try to provide a general overview of what has been studied and what has not. This "highlights" narrative may include a comment on the relevance of any particular endpoint/route/duration, when applicable.

3.12.2 Identification of Data Needs

Present human data (inhalation, oral, and dermal) before animal data (inhalation, oral, and dermal). For each of the three exposure routes (inhalation, oral, and dermal) for which insufficient data have been identified, additional studies should be proposed.

The subsections that must be discussed (in order) beneath this dummy heading are the following.

Acute-Duration Exposure

-Is there sufficient information in humans (or several animal species) to identify target organs following exposure via all three routes? Do the animal data support the human data? Comment, as necessary, on the appropriateness of the animal species. *Remember that the emphasis is on target organs in humans.*

-State whether the data were sufficient to derive oral and inhalation MRLs. If not, state what information is lackingCeither inadequate identification of target organs or levels of exposure (LOAELs or NOAELs) that cause the effect.

-In the absence of route-specific toxicity data, state whether pharmacokinetic data are available that may support the identification of target organs across routes of exposure. The end result may be that qualitatively we would expect similar endpoints, but the levels (that cause the effects) may or may not be possible to predict.

-Lethality data are generally needed only to place other toxicity information into perspective; it is unlikely that additional lethality data will ever be requested.

-State what additional route-specific exposure information is necessary.

-Purpose: There are populations surrounding hazardous waste sites who might be exposed to the substance for brief periods; therefore, this information is important.

Intermediate-Duration Exposure

-Same as Acute-Duration Exposure items 1-5.

-Purpose: There are populations surrounding hazardous waste sites who might be exposed to the substance for similar durations.

Chronic-Duration Exposure and Cancer

Chronic toxicity data and carcinogenicity data should be discussed in order using two separate paragraphs.

Chronic Toxicity Data:

-Same as Acute-Duration Exposure items 1-5.

-Purpose: There are populations surrounding hazardous waste sites who might be exposed to the substance for similar durations.

Carcinogenicity Data:

-Discussion should focus on the qualitative evaluation of carcinogenic potential across routes of exposure and the mechanism(s) of action.

-Regarding mechanism(s) of action draw needs from peculiarities noted in the data, i.e., bolus versus nonbolus effects, vehicle effects, initiation versus promotion, route-specificity, etc.

-In the absence of route-specific data, state whether pharmacokinetic data may support the carcinogenic potential of the substance across routes of exposure.

Because the Agency has not formally adopted a nonthreshold policy for carcinogens or the use of modeling to derive low-level risks, it is not appropriate to request additional studies for purposes of generating data necessary for modeling.

Genotoxicity

-Do human data indicate whether the substance may act by a genotoxic mechanism?

-Do *in vivo* animal data (and/or *in vitro* studies) lend support to the substance's genotoxic potential?

-In the absence of genotoxicity data, are there "structural alerts" (e.g., electrophilic centers) that suggest the substance is genotoxic?

-What additional *in vivo* and *in vitro* studies would be important to either confirm or refute the substance's genotoxic potential? If either the *Salmonella* mutagenicity test or an *in vitro* test for chromosome aberrations is positive, consider requesting *in vivo* tests of chromosome aberrations in (known) exposed humans or animals.

-If genotoxicity testing has only been performed at the maximum tolerated dose (MTD), consider suggesting lower dose values.

Reproductive Toxicity

-When developing this discussion, remember that the Agency places extreme importance on the acquisition of reproductive toxicity data; in fact, it is desirable to have such data from inhalation and oral routes prior to developing MRLs.

-State whether there is sufficient information in humans (or several animal species) to indicate whether the substance affects reproductive health following exposure via all three routes. Do the animal data support the human data? *Remember that the emphasis is on human health significance.*

-In the absence of route-specific data, state whether pharmacokinetic data may support the substance's potential to affect reproduction across routes of exposure. The end result may be that qualitatively we would expect similar health outcomes, but the levels (that cause reproductive effects) may or may not be possible to predict.

-If intermediate-duration (90-day) studies are needed, consider including discussion of this data need, i.e., reproductive organ pathology should be examined in the 90-day study.

-Multigeneration studies could be recommended after data are available to indicate that the reproductive system might be a target organ.

Developmental Toxicity

-Similar to reproductive health outcomes, the Agency places importance on assessment of developmental toxicity; it is desirable to have such data from inhalation and oral routes prior to developing MRLs.

-State whether there is sufficient information in humans (or in several animal species) to indicate whether the substance affects development following exposure via all three routes. Do the animal data support the human data? *Remember that the emphasis is on human health significance.*

-In the absence of route-specific data, state whether pharmacokinetic data may support the substance's potential to affect development across routes of exposure. The end result may be that qualitatively we would expect similar health outcomes, but the levels (that cause the effects) may or may not be possible to predict.

The discussion in this subsection should be closely coordinated with the text in the Children's Susceptibility Data Needs subsection. Authors should answer the following questions.

- Are data adequate on whether the developmental process is altered by [Chemical X]? In humans? In immature animals from embryos up through maturity? In in vitro developmental models? Note that developmental problems may include functional neurological development, such as learning deficits and deficits in social behavior. Please remember that development starts at conception and isn=t complete until sexual maturity in animals, or by definition, 18 years of age in humans. This section should address data needs related to both prenatal and postnatal exposures and prenatal and postnatal development.

Immunotoxicity

-Is there reason to believe that the immune system is a target for this substance, either from empirical data or from references from related substances? For example, were there any effects on lymphoid tissue or blood components (peripheral lymphocytes) in the 90-day study? If the answer is a resounding "no," it may be possible to conclude that no additional information is needed at this time.

-If the answer above is "yes" (please refer to the section where Immunological and Lymphoreticular Effects are discussed), has a battery of immune function tests been performed?

-Is there any reason to suspect the effects may be route- or species-specific?

Neurotoxicity

-Is there reason to believe that the nervous system is a target for this substance, either from empirical data or from inferences from related substances? Specifically, is there behavioral, histopathological, neurochemical, or neurophysiological information? If not, it may be possible to conclude that no additional information is needed at this time.

-Is there any reason to suspect the effects may be route- or species-specific or age-dependent?

-If there a substance is an adult neurotoxin, developmental neurotoxicity should be studied.

Epidemiological and Human Dosimetry Studies

-Describe any human studies that are currently available and their limitations.

-Is there likely to be an identifiable subpopulation in the general populace and/or in the workplace potentially exposed to the substance?

-Discuss the type of study that might be proposed, and highlight endpoints for which there is information from animal studies or from case studies suggesting that those endpoints may be of concern.

-Relate how this information will be useful for establishing cause/effect relationships and future monitoring of individuals living near hazardous waste sites.

Biomarkers of Exposure and Effect

Chapter 1 of *Biological Markers in Reproductive Toxicology* (NAS/NRC 1989) provides a good general discussion of this topic. A copy of this reference is being provided to each contractor. This data need should contain the following two subheadings.

Exposure. A biomarker of exposure is an exogenous substance, or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured within a compartment of an organism (e.g., measurement of the parent compound or its metabolite(s), DNA adducts, etc.).

-Identify known biomarker(s) of exposure for the substance, and state what biological materials should be monitored to determine (a) short-term exposure, (b) intermediate-term exposure, and (c) long-term exposure.

-State whether the identified biomarkers are specific for the substance (e.g., metabolites).

-If the parent compound(s) or its metabolite(s) are the only known biomarkers, discuss the usefulness of developing alternative biomarkers to complement this analysis (e.g., sensitivity may be a problem, and you may wish to refer the reader to Chapter 7, Analytical Methods).

-Keep in mind that the purpose for developing a biomarker is often to facilitate future medical surveillance, which can lead to early detection and possible treatment.

-Identify the data needs and why they are needed.

Effect. For the purpose of this data need, a biomarker of effect is a measurable biochemical, physiological, or other alteration within an organism that, depending on the magnitude, can be recognized as an established or potential health impairment or disease.

-Identify known biomarker(s) of effect (i.e., enzyme levels, lymphocytes, aberrations) for the substance, and state what biological materials should be monitored to determine effects resulting from (a) short-term exposure, (b) intermediate-term exposure, and (c) long-term exposure. State whether the biomarker can be used for dosimetry or is only indicative of effect.

-Identify the data needs and why they are needed.

Absorption, Distribution, Metabolism, and Excretion

This data need should discuss these parameters by route and duration of exposure; the subsequent data need should describe toxicokinetics across species.

-Is information available to assess relative rates and extent of ADME regarding the three routes of exposure?

-Are there differences in ADME regarding time or dose, i.e., do saturation phenomena come into play?

Comparative Toxicokinetics

This data need should examine toxicokinetics across species; the preceding data need (ADME) should describe route- and duration-specific pharmacokinetic needs.

-Are both human and animal data available and do they indicate similar target organs?

-Have toxicokinetic studies been performed in both humans and animals? What do these studies show, i.e., are rats a good model?

-Have toxicokinetic studies been performed in multiple species? If so, are results similar, and would it be reasonable to expect humans to handle the substance similarly (and have similar target organs)?

Methods for Reducing Toxic Effects

This data need should examine the existing clinical and experimental methods of reducing both short- and long-term toxic effects of exposure.

-Is the mechanism(s) of absorption of the substance known? If so, are there established methods or treatments for reducing absorption following exposure? Note that these methods are useful only immediately following exposure to the toxic substance. If the mechanism(s) is not known, state this as a data need. Is the mechanism(s) of distribution of the substance in the body known? If little is known regarding distribution of the substance, state this as a data need.

-Are there established methods or treatments for reducing body burden of the substance or toxic persisting metabolites? Are these methods sufficient to prevent toxicity following long-term exposure?

-Is the mechanism of toxic action of the substance known? If not, state this as a data need. If the mechanism of toxic action is known, are there established methods that block this mechanism of toxic action?

-Are there established methods for mitigation of the health effects that result from exposure? For example, are there treatments to repair damage or improve compromised function?

Children's Susceptibility

The discussion in this subsection should be closely coordinated with the text in the Developmental Toxicity Data Needs subsection. The following questions should be addressed, with explanations where necessary.

- Have children or immature animals that have been exposed to [Chemical X] been adequately studied for health effects? Is there a need for such data? Is there a need to determine if health effects due to [Chemical X] can be observed in adults exposed as children?

- Are there any specific theoretical reasons for thinking that children would differ from adults in their vulnerability? Are data adequate to know whether the susceptibility of children to the health effects from [Chemical X] actually differs from that of adults? Is there a data need to investigate the susceptibility of children to health effects caused by [Chemical X]? Explain why or why not.

- Refer the reader to the Developmental Toxicity Data Needs subsection, with the boilerplate statement: "**Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during**

childhood, are discussed in detail in the Developmental Toxicity subsection above." Sometimes studies designed to observe developmental effects may also identify nondevelopmental health effects during childhood, and vice versa. Where both purposes can be served by a single study, this should be noted in the text.

- Is experimental evidence adequate to evaluate whether pharmacokinetics are different in children, or is this a data need? Are data adequate on whether [Chemical X] or its active metabolites can cross the placenta or be excreted in breast milk? Are data adequate to know whether [Chemical X] is stored in maternal tissues during preBconception exposure, and whether any of these stores can be mobilized during pregnancy or lactation? Are there adequate animal data on any of these issues? Are there PBPK models for children, embryos/fetuses/pregnant women, infants/lactating women, or adolescents? Is there a need for this type of model?

- Is experimental evidence adequate to evaluate whether metabolism is different in children or the developing fetus than in adults? Is this a data need? Have any studies in animals been done that might suggest that metabolism might be different in children or the developing fetus than in adults? If the key enzymes metabolizing [Chemical X] have been identified, is their expression generally known to differ in children or fetuses compared with adults? Is there a need for information on the specific metabolism of [Chemical X] in children or fetuses compared with adults? Are there any data needs related to placental metabolism?

  - Is evidence adequate to evaluate whether the mechanism of action is different in children, developing embryos and fetuses, or immature animals? Is this a data need?

  - Is there any reason to suspect that parental exposure might affect children? Are data adequate to determine if this is the case? Explanations may be necessary to describe pharmacokinetics and metabolism in relation to parental germ cells, the genotoxic potential of [Chemical X] or its metabolites, the ability of [Chemical X] or its active metabolites to cross the placenta or accumulate in breast milk, or the ability of [Chemical X] to indirectly affect the fetus during maternal exposure.

  - Discuss any issues related to childhood cancer and either prenatal or postnatal exposures to [Chemical X].

  - Have any biomarkers of exposure or effect been validated in children or adults who were exposed to [Chemical X] during childhood? Is this a data need? If there are no biomarkers in adults, it may be appropriate to suggest that the development of biomarkers for the general population should take precedence over developing or validating biomarkers in children.

  - Are data sufficient to determine whether there are any interactions with other chemicals that are unique to children or whether interactions observed in adults occur

in children? Is this a data need? Have interactions been observed in immature animals?

- If any methods are used in adults to reduce peak absorption after exposure, reduce body burden, or interfere with the mechanism of action for toxic effects, are there adequate data on whether these methods work in children? Do pediatricBspecific methods for reducing peak absorption after exposure, reducing body burden, or interfering with the mechanism of action for toxic effects need to be developed?

Add the following Boilerplate (**bold**) to the end of the discussion in this section:

Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

The headings should be bold, indented, and followed by a period. Text should begin after two spaces. Further guidance on the proper style, tone, and content of these data-need sections is provided in the editor's guidelines of this document and in Exhibit 28.

Data Needs for Modeling

Additional laboratory studies may be needed to provide information on the following physiological and biochemical parameters as they relate to [substance x] in a specific mammalian species, as well as on the physicochemical properties of the chemical.

Physiological parameters:

- Volumes of organs.
- Alveolar ventilation.
- Cardiac output.
- Perfusion rates.

Biochemical parameters:

- Determination of biochemical parameters of enzyme processes, such as V_{max} and K_m.
- Metabolic clearance.
- Excretory clearance.
- Binding and reactivity.
- Absorption constants.
- First-pass effects.

- Parameters that can influence rate of elimination and bioavailability.
- Inhibition rate constants and dose/elimination rates.

Physical and chemical properties of the chemical:

- Blood:air and tissue:blood partition coefficients.

Solubility:

- Saturated vapor pressure.

3.12.3 Ongoing Studies

This section should tabulate and/or discuss any ongoing research pertaining to the topics covered in Chapter 3.

Identify databases and ways to locate additional information. This is important, because there may be studies in progress that will fill a gap or need.

REFERENCES:

ATSDR. 1989. Agency for Toxic Substances and Disease Registry. Federal Register 54:37618-37634.

EPA. 1988. Recommendations for and documentation of biological values for use in risk assessment. Cincinnati, OH: Environmental Criteria and Assessment Office. EPA/600/6-87/008 (February).

EPA. 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Washington, DC: Office of Research and Development. EPA/600/8-90/066F.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

This chapter is divided into the following two sections:

4.1 Chemical Identity
4.2 Physical and Chemical Properties

The introduction to Chapter 4 should include a discussion/interpretation of pertinent information provided in the tables that follow. This should summarize the expected behavior of the chemical in biological or environmental media based on its chemical/physical properties. For example, a high Koc would indicate that the chemical would tend to bioaccumulate; high water solubility would indicate that the chemical might find its way into groundwater. From the chemical/physical properties known, what can you say about the chemical in terms of its behavior upon release to the environment, or after assimilation into an organism.
These sections should contain practically no text (text may be needed where several forms, compounds, or isomers are discussed in the profile). All other information should be presented in tabular form. Include all standard items as illustrated in Exhibits 18 and 19. If there is no information, use either "No data" or "ND" in the table; "ND" should be defined as "No data" in the footnote. If the information is not relevant, use "NA" and define it in the footnote as "Not applicable." Do not use "No data" if the information is not relevant.

In profiles containing information that cannot fit onto one portrait-style (vertical) page, the tables should be presented landscape-style (horizontally) as shown in Exhibits 18 and 19.

The selection of chemical forms (e.g., ionic species, complex) to include in the tables should be made after considering the forms reported in monitoring data or those likely to be found at NPL sites, and the forms important in the fate and transport of the substance in the environment. All compounds discussed in Chapter 3 (including LSE tables) should be included. *Note: Discuss substances for which only lethality data have been obtained with the chemical manager.*

4.1 CHEMICAL IDENTITY (EXHIBIT 18)

Restrict synonyms and trade names to a reasonable number in Table 4-1. Select those that are most common or most distinctive. If additional synonyms or trade names are listed in the reference, indicate this by putting "and others" at the end of the list in the table.

4.2 PHYSICAL AND CHEMICAL PROPERTIES (EXHIBIT 19)

More than one value may be cited for any of the properties listed in Table 4-2 with reference(s). For inorganic compounds, valence state should be included in the table. National Fire Prevention Association (NFPA) classifications for flammability and reactivity may be very useful. If they are used, the number can be given and a definition provided in the footnote. Use the NFPA (1994) Fire Protection Guide for Hazardous Materials, 11th edition, Batterymarch Park, Quincy, MA, or most recent edition.

Table 4-2 may include reactivities/incompatibilities with other substances and other class- or substance-specific information where appropriate. For example, if the substance reacts violently with water, this fact should be noted. This information should be included under the "Other" category.

Other chemical identifiers and properties also may be included Table 4-2 (see next paragraph), but the properties shown in the example must appear (see Exhibit 19).

Because the chemical form of many pollutants is a prime determinant of their ultimate toxicological behavior, information that permits some quantitative or at least qualitative distinction to be made between chemical forms is very important. Therefore, additional information should be added to Table 4-2 to reflect parameters that may affect toxicity/environmental fate from abiotic transformation processes. This information should be substance-specific and tailored to the profiled substance; that is, the information for a metal such as chromium may be quite different than that for an organic pesticide such as parathion.

For example, the following identifiers and properties might be contained in Table 4-2 for chromium.

- Possible environmental oxidation states and associated species: Cr (III), Cr (VI), CrO_4^{2-}, $Cr_2O_7^{2-}$

- Associated redox potentials.

- Precipitation equilibria.

In comparison, the following might be contained in Table 4-2 for parathion.

- Abiotic hydrolysis rate constants and products of such hydrolyses.

- Oxidation reactions, products, and rate constants under environmental conditions.

- Soil and sediment binding parameters.

- Groundwater retardation constants.

- Complex equilibria with common metals such as Ca^{2+}.

- If the substance is an acid or base, pK_a/pK_b values.

As a result, the contents of Table 4-2 will differ from profile to profile. The additional information should not be a simple listing of the identifiers and properties listed above, but rather a compilation of substance-specific information. Substance-specific information should be compiled, after a scientific evaluation of relevant information that would assist in assessing human health risks from environmental exposure.

CHAPTER 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Keep the level of detail in this chapter appropriate to an overview. The text should be brief (two to three pages) and should summarize the most pertinent information. Figures for production, use, import, export, and disposal should be the most recent. Possible sources for this information include:

- U.S. International Trade Commission (USITC),

- Stanford Research Institute, Incorporated (SRI). (Menlo Park, CA; Directory of Chemical Producers of the United States)

- *Chemical Marketing Reporter* (CMR) (Schnell Publishing, New York, NY)

- *Chemical and Engineering News* (C&EN), (Facts and Figures for the Chemical Industry and Top 50 Chemical Products)

- U.S. Department of Interior, Bureau of Mines (Mineral Commodity Annual Summaries and Mineral Yearbooks) and

- U.S. Department of Commerce (DOC) (U.S. general imports for consumption).

Restrict discussion to major use categories, import quantities, and domestic production processes and quantities unless other topics substantially affect human exposure and health. Present information in narrative form; avoid extensive listing of tabular information. Reference citations for quantitative information on production, import/export, use, and disposal volumes should be cited to appropriate primary or secondary reference sources. Citations to the Hazardous Substances Data Bank (HSDB) are appropriate and may be the only source of information on historic production, import/export or use volumes for some chemicals.

5.1 PRODUCTION

This section should cover the following aspects of production of the profile chemical:

- Production methods (general, few details)

- Production volumes (past, present, and/or trends)

- Information on production and processing facilities as shown in Table 5-1 (Exhibit 20)

Display the most recent year's data from the Toxics Release Inventory (TRI) in Table 5-1 as shown in Exhibit 20. Sort facilities by state. If the TRI listings for individual production and processing facilities (page 1 of Exhibit 20) are longer than 3 pages, then the summary information on facilities presented alphabetically by state as shown in pages 2 and 3 of Exhibit 20 should be used in the profile. The information to be included in these two versions of Table 5-1 is listed below.

- Information on individual production and processing facilities as shown in Table 5-1 (page 1 of Exhibit 20) includes:

    - Facility name
    - Location (city, state)
    - Range of maximum amounts on site in pounds
    - Activities and uses

- Summary information on production and processing facilities as shown in Table 5-1 (pages 2 and 3 of Exhibit 20) includes:

    - State postal abbreviation
    - Number of facilities in each state
    - Range of maximum amounts on site in thousands of pounds
    - Activities and uses

If the profile chemical is not required to be reported to the Toxics Release Inventory, the following boilerplate should be used.

No information is available in the TRI database on facilities that manufacture or process (name of profile chemical) because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-

Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 1997).

Cite the most recent version of the report entitled *Toxic Chemical Release Inventory Reporting Form R and Instructions*. U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, D.C. EPA 745-K-97-001.

This section should primarily deal with production of the profile chemical from manufacturing or mining processes and/or any similar anthropogenic sources. This section should not include reference to inadvertent production of a chemical (i.e., as a by-product in the production of another chemical or as a product of some anthropogenic process such a combustion of fossil fuels or natural process such as volcanic activity, forest fires, or sources such as the unintentional production of ammonia by livestock. These other sources should be covered in the appropriate sections of Chapter 6 (Potential for Human Exposure), particularly in Section 6.2 (Releases to the Environment).

5.2 IMPORT/EXPORT

This section should cover the following aspects of U.S. trade:

- Import volumes (past, present, and/or trends)
- Export volumes (past, present, and/or trends).

5.3 USE

This section should cover the following aspects of industrial, commercial, and consumer uses for the profile chemical:

- Past uses
- Present uses

- Approximate amounts by use or percentage of production by use

5.4 DISPOSAL

This section should cover the following.

- Rules and regulations regarding disposal practices (refer to Chapter 8, Regulations and Advisories).

- Typical methods of disposal (including biological waste treatment and other new treatment and disposal technologies) (refer to Section 6.2 Releases to the Environment)

- Amounts of substance disposed of by each means

- Past disposal, present disposal, and/or disposal trends (refer to Section 6.2, Releases to the Environment)

- Information on recycling and/or reuse of the substance

CHAPTER 6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

The overview summarizes the information in this chapter. Use general statements describing the ways in which releases to air, water, and soil are modified by time and environmental fate processes, and the potential for human exposure to the substance via the different pathways. The locations of National Priority List (NPL) hazardous waste sites contaminated with the substance should be identified geographically on a map of the United States, as shown in Exhibit 21. The contractor will construct the map using the HazDat database.

When noncontinental U.S. NPL sites (with the exception of Hawaii and Alaska) are identified, they are indicated in the text with language patterned after the following.

> **[Substance x] has been identified in at least ___ of the 1,613 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 200_). However, the number of sites evaluated for [substance x] is not known. The frequency of these sites can be seen in Figure 6-_. [Use the following only if some sites are in Puerto Rico.] Of these sites, ___ is/are located in the United States and ___ is/are located in the Commonwealth of Puerto Rico (not shown).**

Note: In addition to sites in the Commonwealth of Puerto Rico, this last sentence should identify sites in any of the other three U.S. territories (American Samoa, Guam, and the U.S. Virgin Islands) as appropriate. The phrase "not shown" should always be put at the end of the sentence, as maps for NPL sites in any of the U.S. territories are not available.

Note: Modification of the boilerplate will be required for profiles with more than one map.

The contractor and ATSDR should work together to determine the best method of presenting NPL information (maps and text) in profiles that cover more than one chemical form, compound, or radioactive isotope.

Throughout Chapter 6, cite primary references where possible, and avoid citing the Hazardous Substances Data Bank (HSDB). However, HSDB may be used if primary references on historic releases to the environment cannot be located. Express air concentrations in the same units as those used in the Chapter 3 inhalation LSE table. There should be consistency regarding units used for reporting data in a given environmental medium throughout this document, including Table 8-1. Note: Units shown in Chapter 8 will be those presented in the cited international, federal, or state guidelines and advisories. As appropriate, conversions to units shown in Chapters 3 and 6 will be shown in paratheses.

As in other chapters, the units reported should be those used in the cited reference. Results for a given medium should be expressed in the same units (for example, mg/L, mg/kg, mg/m^3; that is weight-to-volume or weight-to weight) whenever possible. Use of a single standard unit for a given medium may, however, result in unwieldy numbers because of the wide range of concentrations that often occurs when comparing samples from the same medium collected at pristine vs. contaminated sites. For comparability of units within a given medium, it is recommended that conversions with the same units in the denominator (e.g., L, kg) and units in the numerator (e.g., ng or mg) that result in the smallest numerical value be used. As an example, for sediments, concentrations such as 100 to 11,000 ng/g may occur in ambient sediment, while 1,900 mg/kg concentrations occur at a hazardous waste site. Converting the concentrations at the hazardous waste site to the units used for the ambient range (ng/g) would yield 1,900,000 (or $1.90x10^6$) ng/g. It would be better to use the same units in the denominator, while using the unit resulting in the smallest number of digits in the numerator. For example 100 to 11,000 ng/g would become 0.1 and 11 µg/g respectively and 1,900 mg/kg would become 1.9 mg/g. Values for ppm and ppb may be used as the standard units for a given medium; but they must always be used with w/v or v/v in parentheses when they are required for comparability with inhalation LSE tables. Also, because not all of the chemical(s) present in a certain matrix may be bioavailable to act as toxicants, a statement should be included (especially for contaminated soils, subsoils, and sediments) that the amount of the chemical found by analysis is not necessarily the amount that is toxicologically available. The following boilerplate statement is suggested.

It should be noted that the amount of (profile chemical name or names) detected by chemical analysis is not necessarily the amount that is bioavailable.

6.2 RELEASES TO THE ENVIRONMENT [DUMMY]

This section is divided into three subsections.

6.2.1 Air
6.2.2 Water
6.2.3 Soil

To evaluate the potential for ambient exposure to a substance, it is necessary to trace the substance from its point of release to the environment until it reaches the receptor population. These subsections summarize information pertaining to environmental releases from sources such as natural occurrence(e.g., volcanic activity or other natural chemical/ biological processes, chemical production processes, and end-user use and disposal, as well as diffuse sources such as fossil fuel combustion from electric generating facilities, auto emissions, household product use, and storm drain and agricultural runoff. Although the sources of the pollutant from production and processing facilities and major uses are discussed in Chapter 5, briefly referring to them here will be necessary. Search TRI (the latest year reported) and the published literature. Use information from the ATSDR HazDat database on the media (air, surface water, groundwater, soil, and sediment) in which the pollutant has been detected at NPL hazardous waste sites. Releases to all media (air, water, and soil) should be discussed. When presenting information, the reported values should be used and comparable units provided in parentheses. Note any differences in estimates reported and the facilities, point/nonpoint sources, etc., that were included in the estimates. Note: Do not include data from a contract laboratory statistical database.

The following sentence should be used in Sections 6.2.1, 6.2.2, and/of 6.2.3 only if information is available on POTW treatment removal efficiencies for the profile chemical:

The TRI data should be used with caution because only certain types of facilities are required to report (EPA 1997). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the Toxics Release Inventory only if they employ 10 or more full-time employees; if their facility is classified under Standard Industrial Classification (SIC) codes 20 through 39; and if their facility produces, imports, or processes 25,000 or more pounds of any TRI chemical or otherwise uses more than 10,000 pounds of a TRI chemical in a calendar year (EPA 1997).

If no TRI information is available for the profile chemical for Sections 6.2.1, 6.2.2, and/or 6.2.3, the following statement should be used.

There is no information on releases of [substance x] to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 1997).

TRI Tables

Display data from the most recent TRI as shown in Table 6-1 (Exhibit 22). The TRI data format differs from that used in previous ATSDR profiles. As shown on page 1 of Exhibit 22, the column headings should present information in the following order: state, city, facility, and reported amounts released in pounds per year for air, water, land, underground injection, total environment, publicly owned treatment works (POTW) transfer, and off-site waste transfer. Enter the information in alphabetical order by state. Report information from all individual facilities unless too voluminous (3 pages or more). If this is the case, use the summary report of all facilities in each state as shown in Table 6-1 on pages 2, 3 and 4 of Exhibit 22. This summary table should contain state information alphabetized by state, and the number of facilities per state or each of the release categories (air, water, land, underground injection, total environment, POTWs, and off-site waste transfer.

Look carefully at the data displayed in detailed version of Table 6-1 for all media (air, water, soil, underground injection) as well as the amount that is transferred to POTWs and the amount

that is transferred off-site. Report any trends that may be present in the narrative text for the respective medium (air, water, soil). For example, if the largest percentage of environmental releases are to the air, then the potential for exposure via inhalation to these releases should be assessed in Section 6.5 (General Population and Occupational Exposure). Also, if certain facilities released large amounts via underground injection, this should also be discussed under disposal (Section 5.4).

When presenting TRI data (summation of all states) in the narrative text for total releases for air, water, soil, and underground injection, include the total amount released for each and the relative amount (%) of the total environmental release that each contributed. Examples are provided below for air, water, and soil for use in the discussions for Sections 6.2.1, 6.2.2, and 6.2.3 respectively.

6.2.1. Air

Estimated releases of XXX million pounds (~ metric tons) of [substance x] to the atmosphere from (insert total number of facilities reporting to TRI) domestic manufacturing and processing facilities in 20__, accounted for about ___% of the estimated total environmental releases (TRI[*insert2-digit year]*__ 20__). These releases are summarized in Table 6-1.

6.2.2. Water

Estimated releases of XXX million pounds (~ metric tons) of [substance x] to surface water from (insert total number of facilities reporting to TRI) domestic manufacturing and processing facilities in 20__, accounted for about __% of the estimated total environmental releases (TRI[*insert2-digit year]*__ 20__). An additional XXX million pounds (~ metric tons), were released to publicly owned treatment works (POTWs) (TRI9_ 199_). These releases are summarized in Table 6-1.

Use the following sentence only if information is available on POTW treatment removal efficiencies for the profile chemical.

As a result of secondary treatment processes in POTWs, only a small % (__ %) of substance x that enters POTWs is subsequently released to surface water. This information is available for some chemicals in the open literature.

Note: Information from TRI should be qualified by the following statements.

The TRI data should be used with caution because only certain types of facilities are required to report (EPA 1997). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the Toxics Release Inventory only if they employ 10 or more full-time employees; if their facility is classified under Standard Industrial Classification (SIC) codes 20 through 39; and if their facility produces, imports, or processes 25,000 or more pounds of any TRI chemical or otherwise uses more than 10,000 pounds of a TRI chemical in a calendar year (EPA 1997).

Note: if no TRI information is available for the profile chemical, the following statement should be used.

There is no information on releases of [substance x] to water from manufacturing and processing facilities because these releases are not required to be reported (EPA 1997).

6.2.3. Soil

Estimated releases of XXX million pounds (~ metric tons) of [substance x] to soils from (insert total number of facilities reporting to TRI) domestic manufacturing and processing facilities in 20_9_, accounted for about ___% of the estimated total environmental releases (TRI[*insert2-digit year]*_ 20__). An additional XXX million pounds (~ metric tons), constituting about ___% of the total environmental emissions,

were released via underground injection (TRI[*insert2-digit year]_ _* 20__). These releases are summarized in Table 6-1.

Note: Information from TRI should be qualified using the following statements.

The TRI data should be used with caution because only certain types of facilities are required to report (EPA 1997). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the Toxics Release Inventory only if they employ 10 or more full-time employees; if their facility is classified under Standard Industrial Classification (SIC) codes 20 through 39; and if their facility produces, imports, or processes 25,000 or more pounds of any TRI chemical or otherwise uses more than 10,000 pounds of a TRI chemical in a calendar year (EPA 1997).

Note: if no TRI information is available for the profile chemical, the following statement should be used.

There is no information on releases of [substance x] to soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 1997).

The amount of the chemical waste that is transferred off-site should also be noted (cross reference this to Section 5.4, Disposal).

6.3 ENVIRONMENTAL FATE [DUMMY]

This section is divided into two subsections.

6.3.1 Transport and Partitioning
6.3.2 Transformation and Degradation

6.3.1 Transport and Partitioning

This section is divided into four subsections.

6.3.2.1 Ambient Air
6.3.2.2 Ambient Water
6.3.2.3 Sediment and Soil
6.3.2.4 Bioconcentration and Biomagnification

The purpose of this section is to describe how the substanceCif a metal, the metallic, inorganic, or organic form, with the valence state notedCor its metabolite(s) moves in the environment after its initial release. This should include a discussion of mobility in each medium (air, water, and soil), as well as any tendency to partition from one medium to another (e.g., from water to sediment). Key properties and factors for transport and partitioning include particle size range for particulate pollutants, groundwater retardation factors, log octanol-water coefficient (log K_{ow}), water solubility, log adsorption coefficient relative to organic carbon (log K_{oc}), vapor pressure, and Henry's Law constant. Discuss the form in which the substance exists in air (e.g., in the vapor phase, as a particulate), residence time and transport information, and factors that control its removal (e.g., dry deposition and wet deposition). Information about factors that control removal of the substance from the air is important for assessing bioavailability.

Discussion should include but not be limited to volatilization, sorption, bioconcentration, biotransformation, and bioavailability. Consider all processes that would affect transport and partitioning between air, water, sediment, and soil, and within each compartment (e.g., the potential to leach into groundwater will depend on factors such as K_{oc}, soil type, organic matter, rainfall, depth of groundwater, and extent of degradation). Are there major reservoirs or sinks for the substance? If this information is not known but data exist on properties of the substance that can be used to predict transport and partitioning, make such predictions. However, those predictions should be clearly and specifically designated as estimations in the absence of actual data. Do not speculate. Remember that data needs are to be identified where data are lacking. If applicable, consider a discussion of kinetics, including whether the assumption of first-order kinetics, half-life values (kinetics of disappearance), and persistence (residence time) would affect transport and partitioning between air, water, sediment, and soil, and within each compartment.

Discuss the potential importance of bioconcentration and increases in concentration or appearance in various plants and animals as a result of food-chain magnification. Indicate if these are significant reservoirs or sinks for the chemical. When discussing terrestrial plants, consider the major pathway of vegetation contamination (e.g., air-to-leaf transfer, root uptake, and translocation to aboveground parts of edible plants). The description of bioconcentration potential should include both bioconcentration and bioaccumulation within a single trophic level (i.e., within an organism) and biomagnification (i.e., the potential for a substance to move up the food chain through several trophic levels).

Information on experimentally measured bioconcentration factors (BCF) should be included when available. The species in which the BCF was actually measured and experimental parameters (e.g., duration of exposure, age of organism etc.) should be provided. If measured BCF values are unavailable, estimated BCF values (derived from log K_{ow} or by analogies to structurally related compounds) may be cited, as long as the values are clearly identified as "estimates."

If a chemical is subject to bioconcentration in aquatic organisms, or bioaccumulation by terrestrial plants, or if biomagnification is a potentially important route of human exposure, the available information or estimates of the likely exposure should be presented.

6.3.2 Transformation and Degradation

This section is divided into four subsections.

6.3.2.1 Air
6.3.2.2 Water
6.3.2.3 Sediment and Soil
6.3.2.4 Other Environmental Media

Each subsection should include descriptions of abiotic and biological transformation processes, rates, and products. Information on biodegradation (aerobic and anaerobic), abiotic degradation in surface and subsurface soil and in surface and groundwater, and photochemical and other abiotic degradation in air and water should be included, if available. If this information is not available, this information should be clearly stated; do not provide speculations. Information should differentiate clearly between field and laboratory findings. If the information on biodegradation comes from studies on individual species or mixtures of microorganisms in culture media, this should be stated. Particular attention should be paid to the rates of biodegradation and abiotic degradation in environmental media.

Caution should be exercised when working with half-lives found in the published literature. The disappearance of the more persistent compounds in nature often does not follow half-life kinetics, especially when only a small percentage of the original compound remains or after some time has elapsed. The values predicted by half-life kinetics often differ more and more from the actual values in nature as time progresses. The published values for half-lives are often misleading because they assume first-order kinetics. If half-lives are given in the profile, the text should indicate whether first-order kinetics have really been shown; that is, a half, quarter, eighth, sixteenth, etc., of the substance remains after one, two, three, four, etc., half-lives. Incorrect conclusions on persistence are often reached from misuse of a single datum or an incomplete set of data to calculate half-lives. If the published information contains data showing that the rate of disappearance is indeed first-order, half-lives should be given. If sufficient information is not available on the concentrations remaining with time to show first-order kinetics, citation of a presumed half-life should be qualified with the statement that the half-life represents the calculated time for loss of the first 50% of the substance, but that the time required for the loss of half of that which remains thereafter may be substantially longer, and the rate of disappearance may decline further as time progresses.

Particular attention should also be paid to the products formed during biodegradation or abiotic transformation because some of these products may be more toxic, more persistent, and/or more mobile in nature than the parent substance. The products should be identified, the environmental medium in which they were found should be specified, and their persistence in that medium (to

the extent known) should be stated. If the toxicity of those products to humans or other mammals is known, that fact (together with appropriate references) should be presented. If no actual data exist, useful information on the mobility and persistence of the products may be obtained from the chemical and physical properties of the product or from comparisons to structurally related compounds.

Information on products of environmental transformation can often be presented simply in a figure showing the chemical structures of the products and possible pathways for their formation and interconversion. In some cases, a single figure may be adequate to describe a chemical's transformation and degradation; however, for complex processes, one figure may be required to illustrate atmospheric processes while a second figure is used to show abiotic and biotic processes occurring in water and sediment. This portion of the text on environmental transformation may overlap with the metabolism discussion in Chapter 3; cross references between the two chapters are helpful. The need for thorough exposition of the products of degradation and their transport and fate is made more acute because the degradation products may represent a more serious hazard than the original substance.

The discussion should also include environmental conditions that affect biodegradation or abiotic degradation (for example, dissolved oxygen, pH, organic matter, clay content, temperature, and inorganic nutrients). The effect of such conditions, when known, should be discussed. Other properties that should be considered for inclusion depending on the nature of the profile chemical are as follows:

- Complex equilibria (e.g., with humic substances, ligand formation with ammonia, cyanide)

- Abiotic hydrolysis rate constants and products of such hydrolyses

- Oxidation reactions, products, and rate constants under environmental conditions

- Soil and sediment binding parameters

- Groundwater retardation constants

- Complex equilibria with common metals such as Ca^{2+}

If data are not available on photochemical degradation, use should be made of chemical properties (for example, absorption wavelength) to predict relative degradation rates. However, such calculations should be explicitly described as estimates based on chemical properties only.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT [DUMMY]

As an introduction to this section, a statement should be added that reflects the statement made in Section 6.1 (Overview) that the amount of a chemical detected by analysis is not necessarily the amount that is toxicologically available. Although the statement must be tailored to reflect chemical-specific considerations, the following wording is suggested.

> **Reliable evaluation of the potential for human exposure to substance x depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of substance x in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on [chemical x] levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring substance x in a variety of environmental media are detailed in Chapter 7 (Analytical Methods).**

This section is divided into four subsections.

6.4.1 Air
6.4.2 Water
6.4.3 Sediment and Soil
6.4.4 Other Environmental Media

These major subsections should contain general statements regarding the concentrations of the substance measured in the medium under discussion and potential variations by geographic location. The subsections should include monitoring data obtained in the United States. Provide ranges of concentrations, where possible, as well as means or medians. Express air concentrations in the *same units* as those used in the Chapter 3 inhalation LSE table. As indicated in Section 6.1, whenever possible, the results should be expressed in the same units, with appropriate conversion factors to units that may be more understandable to the lay public or to the news media. There should be consistency regarding units used for reporting data in a given environmental medium.

Data presented should include ambient levels and ranges for indoor air (ambient and industrial levels); outdoor air, (remote, rural, urban, industrial), water (drinking water, surface water, groundwater), soil and sediments, and other media (aquatic organisms and plants, terrestrial animals and plants, birds, food and beverages, cigarettes, mainstream and side stream smoke, consumer products, etc.). Additional sources for this information include the National Oceanic Atmospheric Administration (NOAA), FDA, EPA, the U.S. Department of Agriculture (USDA), U.S. Fish and Wildlife Service (FWS), and the U.S. Geological Survey (USGS), as well as the World Health Organization (WHO), IARC, the International Programme for Chemical Safety (IPCS), and British Health and Safety Executive Reviews (secondary sources).

Ambient or typical background levels should be presented first, followed by levels from media with known contamination. This section should also include monitoring data, where available, from epidemiological studies conducted on environmentally exposed populations that are mentioned in Chapter 3. It is particularly important to include concentrations measured in the vicinity of industrial sources and disposal sites.

The specific form of the substance being measured should be given; to the extent that this information exists ("form" refers to the oxidation state of cations or anions, nonprotonated or protonated or ionic species, chelates, chemical sorbed to environmental surfaces, chemical present in nonaqueous-phase liquids, etc.) Specifying the form is particularly important because

different forms of the same substance often have distinctly different toxicities or environmental transport and fate.

Site-specific or generic information on bioavailability should be presented, if available. Major deficiencies in toxicological evaluations exist because of the lack of information on the bioavailability of chemicals in environmental media. The fact that a given concentration is found at a site does not mean that the concentration found is actually entirely available. The availability may, in fact, vary from 0 to 100%. If sorption, presence in a nonaqueous-phase liquid, or sequestering in environmental matrices is known or is likely to occur for the substance but no data exist on bioavailability, the text should state that the toxicologically significant concentration may be somewhat or substantially less than the concentrations found in soils, subsoils, or sediments.

Identify those data collected by the most reliable and advanced sampling and analytical methods. If there are limitations to the data or reasons to suspect that data may be erroneous due to questionable sampling or analytical methods, this should be stated and a citation provided, if available. If analytical methods are not refined enough to allow for detection in specific media, this should be stated. The subsection should be cross referenced to more detailed information in Chapter 7 (Analytical Methods). Stating such information will aid in assessing data gaps/needs in Section 6.8.1 (e.g., methods are not sensitive enough to measure background levels in air).

If large amounts of environmental monitoring data exist, they can be summarized in an organized fashion in tables that total no more than three pages for each medium. If monitoring information is summarized in tables, separate typical ambient levels from those levels reported from contaminated media. The focus should be on the interpretation of existing data rather than the presentation of six to eight pages of data from various sites.

Modeling studies are occasionally reported in the literature and can be cited in these sections, as long as they are identified clearly as such.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

This section should discuss sources and pathways of exposure for the general population and for people in occupations involved in the production, use, storage, disposal, and cleanup of the substance. Present general population exposure first, followed by occupational exposure. Express air concentrations in the same units as those used in the Chapter 3 inhalation LSE table.

Reported estimates of potential daily intake of the chemical from all routes of exposure should also be included, if available. Indoor and outdoor background exposure levels should be included. For ambient levels of indoor and outdoor air, drinking water and surface water, soil, and food, a table showing percentage exposure from each source for an infant/child, an adult nonsmoker, and an adult smoker (where applicable) might be useful. EPA Total Exposure Assessment Model (TEAM) studies should be used, where available, to show exposure sources and estimated levels for the general population. Where exposures cannot be quantified, they should be described qualitatively. (Physical/chemical properties and speciation, if available, must be included in the assessment of the relative importance of each exposure route and by each source.) Concentrations measured in human tissues and fluids (e.g., blood, serum, urine, feces, organs, breast milk, hair, nails), where available, should also be included in this section. A table can be used to present levels in human tissues and fluids. Body burden data give reliable evidence of human exposure, although it is often difficult to identify the exposure concentrations. Refer the reader to Chapter 3 if autopsy information from case studies is presented there. Include information on levels in human tissues and fluids in order to identify data gaps/needs in Section 6.8.1.

Search for occupational exposure data that reflect current exposure levels in the United States. Occupational exposure data are available from NIOSH (National Occupational Hazard Survey, 1972-74; National Occupational Exposure Survey [NOES], 1981-83; and Health Hazard Evaluations) and OSHA. Try to locate data from more recent years. Address what the NIOSH surveys covered (e.g., NOES provides estimates of the number of workers potentially exposed to substances in the workplace). In addition, identify which occupations are included in the NOES surveys (see Fifth Set Profile for Benzene). The NOES database may be accessed directly or

through TOMES CD-ROM (latest edition) by accessing the Registry of Toxic Effects Chemical Substances (RTECS) file containing the NOES 1983-1986 Occupational Exposure Survey data.

Occupational regulations and guidelines should be provided if available. The current OSHA Permissible Exposure Limit (PEL) for the chemical for an 8-hour workday should be provided where applicable. The American Conference of Governmental Industrial Hygienists recommended Threshold Limit Value (TLV-TWA) and the recommended exposure limit (REL) for occupational exposures (TWA) set by the National Institute for Occupational Safety and Health (NIOSH) should be provided where applicable for the chemical based on a 10-hour average workday and a 40-hour workweek.

6.6 EXPOSURES OF CHILDREN

This section will be introduced with the following boilerplate.

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in 3.7 Children's Susceptibility.

Children are not small adults. A child=s exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child=s behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

The full citation for the reference mentioned in this boilerplate is listed in this guidance modification for **Chapter 9: References**.

The following issues should be addressed in this section. If necessary for clarity, define the specific stages of growth and development to which the discussion applies.

Topics marked by a big bullet (●) must be discussed, if only to say that no information is available. Issues marked by a small bullet (○) should not be discussed if no relevant information is available.

- Are children exposed? Discuss any exposure or body burden measurements made on children.

- ○ Have measurements been made of [Chemical X] or its metabolite levels in amniotic fluid, meconium, cord blood, neonatal blood, or other tissues that indicate prenatal exposure? It may be necessary to skim the epidemiology studies in chapter 3, or consult with the chapter 3 author to answer this question.

- Have measurements been made of [Chemical X] or its active metabolites in breast milk? If so, discuss these measurements here (it is now unnecessary to have this discussion in **6.5 General Population and Occupational Exposure**). This should address exposure both from normal background and from other exposure scenarios.

  Consult with the chapter 3 author (Section **3.3 Toxicokinetics: 3.3.2 Distribution)** and note whether animal pharmacokinetics experiments have demonstrated that [Chemical X] or its metabolites are transferred to breast milk, and if so, in what quantities (zero, trace, significant, large). In other words, would significant quantities of [Chemical X] or its active metabolites be expected in the milk of exposed women based on results with animal studies? Does physiologically based pharmacokinetic modeling (see Section **3.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models**) suggest that significant quantities of [Chemical X] or its active metabolites should be expected in the milk of exposed women? Please let the chapter 3 author know whether

there are measurements of [Chemical X] in human breast milk discussed in this section, so that this may also be mentioned in Section **3.3 Toxicokinetics: 3.3.2 Distribution**.

- Are unique exposure pathways for children known or possible? If applicable, this should include discussions of pica (eating paint chips or other inappropriate substances); handBtoBmouth activity; putting foreign objects in their mouths; tendencies not to wash hands; propensity to accidental poisonings by ingesting household products, pharmaceuticals, cosmetics, folk remedies, and other swallowable items; sniffing household or commercial products; use of childhoodBspecific medications (e.g., head lice treatments); use of playground equipment; tendencies to play in surface water, such as creeks; tendencies to trespass on posted property; and habitation of microenvironments (such as close to the floor) that might contain different levels of [Chemical X]. Do not forget other factors mentioned in the boilerplate. Any quantitative estimates of exposure should be discussed. This should address exposure from both normal background and other exposure scenarios.

- The tendency of young children to ingest soil, either intentionally through pica or unintentionally through handBtoBmouth activity, is well documented. Please discuss whether childhood exposures to [Chemical X] through soil ingestion have been documented. Please discuss the likelihood of such exposures, using information from the remainder of chapter 6, even if significant exposure of children to [Chemical X] has not been studied; i.e., has [Chemical X] been measured in soil? Do significant quantities of [Chemical X] sorb to soil? Does [Chemical X] biodegrade quickly or slowly in soil? Does [Chemical X] volatilize quickly from soil, so that little is likely to be found in surface soil? Is it known how bioavailable [Chemical X] is from soil for ingestion? Does chapter 3 indicate anything about the efficiency (high, moderate, low?) of oral absorption of [Chemical X] in children or adults if it were to be significantly bioavailable from soil?

- Young children often play close to the ground and frequently play in dirt, which increases both their dermal exposure to toxicants in dust and soil, as well as inhalation exposure to toxicants in airborne particulate matter. Please discuss the likelihood of such dermal and

inhalation exposures, using information from the remainder of chapter 6, even if significant exposure of children to [Chemical X] has not been studied (see previous bullet for questions involved in such an analysis). Is it known how bioavailable [Chemical X] is from soil or dust for dermal and inhalation exposures? Does chapter 3 indicate anything about the efficiency (high, moderate, low?) of dermal or pulmonary absorption of [Chemical X] in children or adults if it were to be significantly bioavailable from soil?

Where appropriate, you may summarize the above points in text such as: AChildren may potentially be exposed to [Chemical X] from oral/inhalation/dermal exposure(s) if they play in the soil of contaminated areas such as hazardous waste sites.@

- If [Chemical X] is significantly heavier than air (chapter 4 author should supply you with this information), point out: A[Chemical X] vapors are heavier than air and since young children are closer to the ground or floor because of their height, they may be exposed to more [Chemical X] than nearby adults during accidental exposures.@

- Mention exposures discussed in **6.4.4 Other Environmental Media** (includes foods), **6.5 General Population and Occupational Exposure**, and **6.7 Populations with Potentially High Exposures** that apply to children, and discuss whether these might disproportionately affect children (e.g., because of factors mentioned in the boilerplate). Refer the reader to section 6.5 or 6.7 for other information.

- Are significant dietary exposures likely? Remember that a child=s diet often differs substantially from that of adults. Are children likely to be exposed to different amounts of [Chemical X] through the diet than adults on an mg/kg/day basis? Sometimes the results of FDA market basket surveys and analyses (such as Total Diet Studies) may be helpful.

  Exposure from eating animal products: ONLY discuss data from chapter 6. Because each state, Native American tribe, or U.S. territory chooses its own criteria (e.g., measurement methods for contaminants, and risk assessment models and assumptions) for issuing fish and wildlife advisories, no conclusions in chapter 6 should be based on an

existing fish or game advisory. ATSDR has not investigated the methodologies used by each state, so the agency might or might not agree with specific fish and game advisories.

Exposure from consumption of produce: Consider the potential for residues on or in imported produce.

- Are structural materials of the home (e.g., lead from plumbing, and radioactivity from certain construction materials made of certain mining slags) likely to release [Chemical X]?

- Are children likely to be exposed to significant amounts of [Chemical X] while household products and pesticides are being used by adults? Are children likely to be exposed to pesticides by premature reBentry into treated areas? For example, there have been multiple papers about measurement of chlorpyrifos residues on children=s toys and the floor and carpet where they may crawl after waiting the specified reBentry time.

- Are children likely to be exposed to [Chemical X] because of its use on pets?

- Are parents' lifestyles or cultural practices (e.g., use of mercury in occult practices such as Santeria, Voodoo, and Espiritismo; use in folk remedies for stomach disorders in Indian and Asian populations; or use of lead in certain folk remedies and cosmetics) likely to be a source of exposure to children?

- Are children more or less exposed than adults to [Chemical X]? Have measurements and calculations been done to determine whether children are different in their weightBadjusted intake of the toxicant?

- Are the parents= working clothes, skin, hair, tools, or other objects removed from the workplace likely to be a source of exposure to children? Please be very clear in distinguishing actual observations of takeBhome exposure from any discussions of theoretical reasons why takeBhome exposure might or might not occur.

TakeBhome or secondary exposure from parental jobs is particularly likely to be a problem with lead and asbestos. See *Report to Congress on Workers= Home Contamination Study Conducted Under The Workers= Family Protection Act* (NIOSH 1995) for a good review of the literature and examples of other chemicals likely to be taken home inadvertently.

- Is the exhaled breath of occupationally exposed parents likely to be a source of exposure for children? Is this exposure likely to be significant (i.e., compare to MRLs or background levels)?

  An example of this is tetrachloroethylene exposure. The following text appears in the Tetrachloroethylene Toxicological Profile. AIndoor air of apartments where dry cleaners lived was about 0.04 ppm compared to 0.003 ppm in the apartments of the controls (Aggazzotti et al. 1994a), indicating that dry cleaners serve as a source of exposure for their families. Breath concentrations of tetrachloroethylene in dry cleaners, family members, and controls were 0.65, 0.05, and 0.001 ppm, respectively (Aggazzotti et al. 1994b). A study which combines PBPK modeling with a single compartment model for a <typical= home (Thompson and Evans 1993) suggests that tetrachloroethylene levels in a home with a worker exposed to a TWA of 50 ppm for 8 hours as the only source of tetrachloroethylene could result in concentrations of 0.004B0.01 ppm. The air exchange rate in the house made a larger difference in the house air concentrations than the choice of metabolic data used in the PBPK model.@ It should be noted that the chronic inhalation MRL is 0.04 ppm.

  References:

Aggazzotti G, Fantuzzi G, Predieri G, Righi E, and Moscardelli S. 1994a. Indoor exposure to perchloroethylene (PCE) in individuals living with dryBcleaning workers. The Science of the Total Environment 156:133-137.

Aggazzotti G, Fantuzzi G, Righi E, Predieri G, Gobba FM, Paltrinieri M, and Cavalleri A. 1994b. Occupational and environmental exposure to perchloroethylene (PCE) in dry cleaners and their family members. Archives of Environmental Health 49:487-493.

Thompson KM, and Evans JS. 1993. Workers= breath as a source of perchloroethylene (PERC) in the home. Exposure Analysis and Environmental Epidemiology 3:417-430.

- Could adolescents, or even younger children, be exposed occupationally? Keep in mind the children of migrant farm workers.

- Are particular incidents (e.g., children playing with mercury) likely to be sources of exposure to children?

- Is inappropriate home use or improper application of pesticides, such as banned and restrictedBuse pesticides, likely to be a source of exposure to children? An example is the series of methyl parathion misuse cases in homes.

- Are children likely to be exposed to [Chemical X] at school? Through arts and crafts?

- If screening of childrenCas a public health practiceCfor exposure to [Chemical X] is appropriate, explain when. What have ATSDR and CDC recommended? Relevant recommendations by EPA, the World Health Organization (WHO), and other agencies may be discussed if appropriate. If possible, provide a brief explanation of the recommended screening test. How is the sample obtained (e.g., by drawing blood or collecting urine)? What is being detected in the test (e.g., [Chemical X], its metabolites, or some other biomarker)? Are there any unique issues relevant to the test? [For example, for blood lead screening, contamination by lead external to the body is an issue. The initial screening is done with capillary blood obtained from a finger prick, and it is particularly important that the finger be adequately cleaned to prevent contamination of the blood sample with environmental lead. A positive initial test is followed up with a venous blood

drawCusually from the arm, which is more difficult and timeBconsuming to do than a finger prick, but less likely to be confounded by contamination with environmental lead from the skin surface of the hand.] Refer the reader to **3.8 Biomarkers of Exposure and Effect** for further details about the test.

- Are there any childhood-specific means to decrease exposure?

When there is information on the class of compounds (such as organophosphates) in which [Chemical X] is included, it may be appropriate to discuss these data and state that "...extrapolating to [Chemical X] would suggest the following...." It may be necessary to do a limited search on the class of compounds and childBhealthBspecific terms to see if such data exist. Authors of chapter 6 should be familiar with both the main literature search strategy and any supplemental search strategies used for [Chemical X] and be able to determine whether these searches are likely to have missed any relevant resources. **Authors of chapter 6 are responsible for instigating any necessary supplemental literature searches [see Literature Search].** The need for a supplemental literature search may become obvious at any time during development of the Toxicological Profile.

Authors of Chapter 6 should be familiar with *Pesticides in the Diets of Infants and Children* (NRC 1993). Authors should *frequently consult this comprehensive review* as they write the child health sections.

The author of section 6.6 will also be a primary contributor to **1.6 How Can [Chemical X] Affect Children?** And **1.7 How Can Families Reduce the Risk of Exposure to [Chemical X]?** And should collaborate closely with the authors of these other sections.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Describe populations that have potentially high exposures, including the potential for exposure (route, pathway, and medium) for populations living around hazardous waste sites contaminated with the substance, manufacturing and processing facilities, or disposal operations (including

underground injection). Remember that the "dose makes the poison," so comparison with ambient data and LOAELS may need to be restated. Consider locations of NPL waste sites contaminated with the substance (Exhibit 21), along with the location of production and user facilities (Exhibits 20 and 22). Discuss these populations and their potential for high exposure first. Consider other populations, groups, or individuals with potentially high exposures and susceptibility to exposure resulting from age infants, young children, and the elderly), special habits (e.g., smoking), behavior (e.g., eating soil), diet (e.g., high fish and wildlife consumption by recreational or subsistence fishers and hunters including Native American populations), activities, religious practices and beliefs, geographic location, use of particular consumer products, medical treatments, etc. Consider passive exposures as well as exposures during active use.

6.8 ADEQUACY OF THE DATABASE [ATSDR BOILERPLATE]

This section begins with the following boilerplate.

> **Section 104(I) (5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of [substance x] is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of [substance x].**
>
> **The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.**

"NTP" should be used the second and third time the boilerplate is included in the profile. It is only necessary to define NTP when first used in the profile.

6.8.1 Identification of Data Needs

The subsections that must be discussed beneath this heading are the following:

Physical and Chemical Properties. .In "Physical and Chemical Properties," the reader can be referred to the tables in Chapter 4, *if appropriate*.

> Do we know enough about the chemical and physical properties (i.e., log K_{ow}, log K_{oc}, Henry's law constant, vapor pressure, etc.) of the substance to permit estimation of its environmental fate?
>
> Indicate the need for confirmation when toxicokinetic, physical, or chemical information is used to predict the fate of a substance.

Production, Import/Export, Use, Release, and Disposal. Insert the following boilerplate in the "Production, Import/Export, Use, Release and Disposal" section.

> **According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 20___, became available in May of 20___. This database is updated yearly and should provide a list of industrial production facilities and emissions.**

In the absence of information on the number of people potentially exposed to the substance near waste sites and other sources, this data need should serve as a surrogate for evaluating human exposure potential. Include an introductory statement based on the information that supports the potential for human exposure to the substance. For example, if the production volume of the substance is high and its usage is widespread in the home, in the environment, and in industry, then the risk for human exposure may be substantial.

Production.

Do we know whether the substance is currently produced and, if so, in what quantity?
Do we know if this amount is larger or smaller than in the past?
Do we know what production might be in the future?

Use.

Do we know whether the substance is widely used in the home, environment, or workplace?
Do we know if it is a food contaminant?

Release.

Considering typical releases of the substance in the home, environment, and workplace, which environmental media are likely to be contaminated with significant quantities of the substance?

Disposal.

Are current disposal methods efficient, and is there a need to improve them?
Is there information on the amounts of the substance disposed of by each method?
Do we know if there are rules and regulations governing disposal of the substance?

Environmental Fate

Do we know whether the substance partitions in the environment? If so, in what media? Do we know whether the substance's mobility has been characterized in soil?

Do we know whether the substance is transported in any environmental medium? If there is no information on the half-life of the substance, this should be considered a data need. To determine the half-life of a substance in water, soil, and sediment, was field testing or microcosms used? Or is the information from controlled lab experiments? How relevant are the data to real-life situations?

Do we know whether the substance is degraded or transformed in each environmental medium? Does it persist in some media? Include the fate of degradation products.

Bioavailability from Environmental Media

State whether the substance is known to be absorbed following inhalation, oral, or dermal contact.

State whether there is any information on absorption (bioavailability) of the substance from contaminated air, water, soil, or plant material. If not, can predictions be made? For example, if a substance is poorly absorbed from the gut and it has a very large

K_{oc} value, can anything be predicted about its bioavailability following ingestion of contaminated soil?

Food Chain Bioaccumulation

Do we know whether the substance is bioconcentrated in plants, aquatic organisms, or animals (i.e., elevated tissue levels indicating storage in the organism as a result of exposure to contaminated media)?

Do we know whether the substance is biomagnified (increased levels in predators resulting from consumption of contaminated prey organisms)?

Exposure Levels in Environmental Media

Has the substance been detected in air, water, soil, plant materials, or foodstuffs? *Remember that the focus is on media surrounding hazardous waste sites.* If not, have any environmental monitoring studies been done? If so, are the data current (within 3 years)? Add the following boilerplate.

Reliable monitoring data for the levels of [substance x] in contaminated media at hazardous waste sites are needed so that the information obtained on levels of [substance x] in the environment can be used in combination with the known body burden of [substance x] to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Have any estimates been made for human intake of the substance from various environmental media?

Exposure Levels in Humans

Has the substance been detected in human tissues such as blood, urine, fat, or breast milk? *Remember that the focus is on populations surrounding hazardous waste sites.* If not, have biological monitoring studies been done? If so, are the data current (within 3 years)? Add the following boilerplate.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Remember that exposures from conception to maturity at 18 years in humans should be covered in this section. The following questions should be addressed.

- Are children exposed? Are exposure and body burden studies on children needed?

- Are there unique exposure pathways for children? Is there a need for studies to explore this issue?

  It may be appropriate to explicitly relate this issue to data needs about bioavailability from soil and dust for oral, dermal, and inhalation exposure from play activities on the ground and soil pica.

- Is it known whether children are different in their weightBadjusted intake of [Chemical X]? In other words, are children more or less exposed to [Chemical X] than adults? Are studies on this issue needed?

- Are there any childhoodBspecific means to decrease exposure? Is this a data need?

Add the following Boilerplate (**bold**) after the discussion in this section:

Child health data needs relating to susceptibility are discussed in 3.12.2 Identification of Data Needs: Children's Susceptibility.

Exposure Registries. The following boilerplate should be added to the "Exposure Registries" section *when appropriate*.

> **No exposure registries for [substance x] were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.**
>
> Are there known populations that may have unusually high exposures to the substance? *Remember that the focus is on populations surrounding hazardous waste sites.* If so, is there a registry of any population that has been exposed to the substance?

6.8.2 Ongoing Studies

Describe ongoing studies related to filling these data gaps. Narrative text like the following may be used.

A search of the most recent Federal Research in Progress (FEDRIP 20_) identified numerous research studies that are currently being conducted that may fill some of the data needs discussed in Section 6.7.1.

For profiles concerning VOCs included on the Third National Health and Nutrition Evaluation Survey (NHANES III) list, the following boilerplate should be included at the beginning of this section.

> **As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, will be analyzing human blood samples for [substance x] and other volatile organic compounds. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.**

For profiles concerning phenolic compounds included on the NHANES III list, the following boilerplate should be included at the beginning of this section.

> **As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environment Health Laboratory Sciences Division of the National Center for Environment Health, Centers for Disease Control and Prevention, will be analyzing human urine samples for [substance x] and other phenolic compounds. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.**

CHAPTER 7. ANALYTICAL METHODS

Include the following text at the beginning of this chapter.

> **The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring [substance x], its metabolites, and other biomarkers of exposure and effect to [substance x]. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter may be those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods may be included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.**

This chapter is divided into the following three sections.

7.1 Biological Samples
7.2 Environmental Samples
7.3 Adequacy of the Database

7.1 BIOLOGICAL SAMPLES

7.2 ENVIRONMENTAL SAMPLES

The purpose of Sections 7.1 and 7.2 is to show the reader, very briefly, the methods that are available for detecting and/or measuring the substance, its metabolites, and other biomarkers of exposure and effects identified in Section 3.6. These sections serve as a quick reference for health officials who need to know which samples are the best for measurement of exposure or for monitoring of effects. They are not intended to provide a full description of the methods or a recommendation to use specific methodologies.

Identify standard analytical methods, emphasizing the most current, reliable, and sensitive methods. State the sensitivity of those methods. Use one system of units for all methods (for example, mg/kg, mg/L) if ppm or ppb are used, their conversion to standard usage (wt/wt or wt/vol) should be specified. Indicate which methods have been standardized by the American Society for Testing and Materials (ASTM), other organizations, or federal agencies. Some examples of sources that should be checked are:

- *Standard Methods for the Examination of Water and Wastewater* (APHA). 1995. 19th edition or most current edition.

- *Methods for the Determination of Organic Compounds in Drinking Water*. EPA Environmental Monitoring and Systems Laboratory, Cincinnati, OH.

- *Methods for Organic Analysis of Municipal and Industrial Wastewater*. EPA Environmental Monitoring and Systems Laboratory, Cincinnati, OH.

- Manual of Analytical Methods (NIOSH). 1994.

- Analytical Methods Manual (OSHA). OSHA Analytical Laboratory, Salt Lake City, UT.

- SW846 Test Methods for Evaluating Solid Waste. 1996. Office of Solid Waste, Washington, D.C.

- Sampling and Analytical Methods of the National Status and Trends Program - National Benthic Surveillance and Mussel Watch Projects 1984-1992. National Oceanic and Atmospheric Administration, Silver Springs, MD.

Discuss important idiosyncrasies of the methods, particularly as they apply to the substance. For example, discuss specificity, precision, accuracy, reliability of each method for showing past exposures, sample stability, etc., as they affect the usefulness of the method for measuring actual or potential exposure to the substance. Include methods for measuring key metabolites and other biomarkers, if that is an acceptable way of measuring exposure. Direct the reader to references that more fully describe the method and sample preparation techniques. If standard reference materials are available and used, this should be indicated.

Use tables to represent analytical methods, including those for metabolites and other biomarkers (Exhibit 23). Where units differ from those reported in Chapters 3 and 6, values should be presented as cited in the reference, with conversions shown in parentheses.

7.3 ADEQUACY OF THE DATABASE [ATSDR BOILERPLATE]

Chapter-specific guidance is given below. This must be read in conjunction with Attachment N (Developing Adequacy of the Database Sections).

7.3.1 Identification of Data Needs

The subsections that must be discussed beneath this dummy heading are:

Methods for Determining Biomarkers of Exposure and Effect

Exposure:

For the biomarkers of exposure identified in the Data Needs section of Chapter 3, state whether existing methods are sensitive enough to measure (a) background levels in the population and (b) levels at which biological effects occur.

Discuss the precision, accuracy, reliability, and specificity of the methods documented. What are the deficiencies in these areas?

Identify the data needed and why they are needed.

Effect:

For the biomarkers of effect identified in the Data Needs section of Chapter 3, if appropriate, state whether existing methods are sensitive to measure (a) background levels in the population and (b) levels at which biological effects occur.

Discuss the precision, accuracy, reliability, and specificity of the methods documented. What are the deficiencies in these areas?

Identify the data needed and why they are needed.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media

The purpose of analytical methods is:

To identify contaminated areas and,

To determine if contaminant levels constitute a concern for human health.

Which media are of most concern for human exposure to the substance?

For each medium, are there methods sensitive enough to measure (a) background levels in the environment and (b) levels at which health effects occur?

Discuss the precision, accuracy, reliability, and specificity of these methods. What are the deficiencies in these areas?

REFERENCES:

NAS/NRC. 1989. Biological markers in reproductive toxicology. National Academy of Sciences/National Research Council. Washington, DC: National Academy Press, 15-35.

7.3.2 Ongoing Studies

For profiles concerning VOCs, insert the following boilerplate.

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, is developing

methods for the analysis of [substance x] and other volatile organic compounds in blood. These methods use purge and trap methodology, high-resolution gas chromatography, and magnetic sector mass spectrometry, which give detection limits in the low parts per trillion (ppt) range.

For profiles concerning phenolic compounds, insert the following boilerplate.

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, is developing methods for the analysis of [substance x] and other phenolic compounds in urine. These methods use high-resolution gas chromatography and magnetic sector mass spectrometry, which give detection limits in the low parts per trillion (ppt) range.

In general, data on regulations and guidelines should be presented in a table (Exhibit 24). Within the categories shown in the table, distinction should be made between air, water, food, and "other." Alphabetize the agencies and organizations. Where carcinogen classifications are cited, briefly define the classification in a footnote on the last page of the table. References should be made to the Code of Federal Regulations or the most recent Federal Register notice.

Information that is relevant but does not fit conveniently into the tabular format can be described in a brief paragraph. The description of clean water effluent guidelines in the tetrachloroethane profile is an example. Also in the text, provide all ATSDR MRLs, the endpoints on which the levels are based, and the reference for the study used to derive the MRL. Follow this with all EPA reference dose (RfD) or reference concentrations (RfC) information (value, endpoint, reference for the study), presented in the same order.

If the profiled substance has been banned for reasons other than human health risks, the profile should explain why. Also, if EPA, NTP, or IARC cancer classifications have not been reported, this should be stated. Units shown in Table 8-1 for international, federal, or state regulations and guidelines are those presented in the cited references. Where units in the cited references are different from those reported in Chapters 3 and 6, values should be presented as cited in the reference, with conversions shown in parentheses. Use the same units whenever possible.

Make sure to include any regulations and advisories that have separate values for children.

Do not forget to include relevant CDC, NIOSH, FDA, OSHA, or other governmental recommendations about [Chemical X] in Table 8-1. *Some of this type of information may not be able to be as presentable in tabular form and should therefore be included in the introductory text of Chapter 8.* For example, CDC recommends targeted blood lead screening of children, rather than universal screening, and state public health departments are responsible for determining which populations are screened. Another example is whether OSHA requires employers to have a Material Safety Data Sheet (MSDS) for [Chemical X]. Authors of other chapters may have suggestions for additional regulations, guidelines, and recommendations that should be included.

Consumption of excess amounts of fish or wildlife contaminated with [Chemical X] may result in significant exposure of children. It is important that all fish and wildlife advisories be obeyed. General information about the existence of fish and wildlife advisories for particular types of fish and game is included in this chapter, so that readers know to consult their state public health or natural resources department for the details.

- FDA recommendations about fish, seafood, or wildlife consumption should be included in the appropriate section of Table 8-1. Include a reasonable amount of detail (i.e., the specific fish, seafood, or wildlife species), along with limits on consumption (i.e., include recommendations to restrict consumption of a certain species to no more than so many servings per month), and any specific recommendations for children or pregnant or lactating women. Note that FDA Action Levels are already reported in Table 8-1. These instructions are aimed at other *recommendations* FDA has made, such as the recommendation about not eating more than one meal a week of shark or swordfish, which, as the predators at the top of the food chain, tend to contain more mercury. *Again, this type of information may be better presented in the text of Chapter 8.*

- Fish, seafood, or wildlife advisories issued by any state, Native American tribe, or U.S. territory that are based on the presence of the profiled substance should be noted in Table 8-1 under:

  State
  Regulations and Guidelines
  c. Fish and Wildlife Advisories:

  AAt least one state, Native American tribe, or U.S. territory has issued a Fish or Wildlife Advisory based on the presence of [Chemical X] in [if fish, just indicate whether freshwater or saltwater, and for all other wildlife list the common name of the species to which the advisory applies (e.g., wood ducks, mallard ducks, turtles, frogs, moose, or woodchucks). No more explicit details should be provided, unless it is a highly unusual advisory. For example, one state has an advisory about consumption of cadmiumBcontaminated moose liver. In such a situation, provide the name of the state, animal species, and the potentially contaminated organ.

  This information, current as of [year], is based on the EPA Fish and Wildlife Advisory Database searched [month and year] on the Internet at http://www.epa.gov/OST/fishadvice/. For more detailed information, consult your state public health or natural resources department. A fish or wildlife advisory will specify the bodies of water or hunting areas with restrictions. The advisory will indicate the species and size of fish or game of concern. The advisory may completely ban consumption or recommend limiting the number of servings of a certain fish or wildlife species to less than a particular frequency. The advisory may indicate that only certain parts of the fish or game should be consumed and recommend preparation methods to minimize exposure. The advisory may have stricter restrictions than for the general public to protect pregnant women, nursing mothers, and young children. Each state, Native American tribe, or U.S. territory chooses its own criteria for issuing fish and wildlife advisories.

Although mercury, polychorinated biphenyls (PCBs), dioxins/furans, toxaphene, and mirex are the most common subjects of fish and wildlife advisories, ALL substances should be checked in the EPA database and with appropriate FDA sources to see if there are fish or wildlife advisories or recommendations based on exposures to [Chemical X]. Note that this database is usually updated in April or May to include data on the previous year=s advisories.

INTERNATIONAL REGULATIONS AND GUIDELINES

Include only guidance from WHO and IARC. Do not include international regulations, either from individual countries or international organizations.

Note: Proposed international standards should not be included.

NATIONAL REGULATIONS AND GUIDELINES

All applicable national regulations and guidelines should be included, whether a number is associated with them or not. For example, include the listing of a substance as a Hazardous Air Pollutant under Section 112 of the Clean Air Act, and include the word "yes" under the column heading "Information." Also include the word Ayes@ under the column heading AInformation@ if a substance is specifically exempted from a statute. Do not include descriptions of those regulations and guidelines that are inappropriate for the substance (e.g., pesticide regulations for substances that are not pesticides). Do not use immediately dangerous to life and health (IDLH) information for NIOSH guidelinesCuse recommended exposure limits (RELs).

Proposed national regulations and guidelines, if available, should be included but identified as proposed. These proposed values should be listed in addition to (not in place of) current values.

STATE REGULATIONS AND GUIDELINES

All applicable state regulations and guidelines should be included, whether a number is associated with them or not.

Note: State-proposed standards should not be included. Sources for information on state regulations and guidelines include:

- BNA Environmental Reporter. State Regulation. Bureau of National Affairs. Washington, D.C.

- CELDs. Computer-aided Environmental Legislative Database System. University of Illinois at Urbana. Urbana, IL.

- FSTRAC. Summary of state and federal drinking water standards and guidelines. U.S. Environmental Protection Agency. Chemical Communications Subcommittee, Federal State Toxicology and Regulatory Alliance Committee.

- NATICH. National Air Toxics Information Clearinghouse. Report on state, local, and EPA air toxics activities. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Research Triangle Park, NC.

- http://www.epa.gov/OST/fishadvice/ for fish advisories

Check to see if any of the following regulations or guidelines apply to the substance in question. This list may not be exhaustive.

INTERNATIONAL

Guidelines:

IARC	Carcinogenic Classification
WHO	Drinking Water Guideline values for Health-Related Organics

NATIONAL

Regulations:

a. Air**:**

Agency/Organization	Information
EPA	NAAQS
	q_1^*
OSHA	PEL (TWA)
	PEL (ceiling)

b. Water:

Agency/Organization	Information
EPA-ODW	MCL

c. Food:

Agency/Organization	Information

EPA-OPTS	TolerancesClist only the range of tolerances for agricultural products
FDA	Action levelsClist only the ranges of various action levels; refer reader to FDA documents for specifics for each food type

d. Other**:**

Agency/Organization	Information
DOT	Hazard Classification
EPA-OERR	List of Hazardous Substances and Reportable Quantities
EPA-OSW	Identification and Listing of Hazardous Waste

Guidelines:

a. Air:

Agency/Organization	Information
ACGIH	Ceiling Limit for Occupational Exposure (TLV-TWA)
NIOSH	Recommended Exposure Limit for Occupational Exposure (8-hr TWA)

b. Water:

Agency/Organization	Information
EPA-ODW	AWQC 1-day Health Advisory (child and adult) 10-day Health Advisory (child and adult) Lifetime Health Advisory (adult) Longer term Health Advisory (child and adult) MCLG SMCL NAS-SNARL EEGL SPEGL

c. Other:

Agency/Organization	Information

ACGIH	Cancer Classification
ACGIH	Biological Exposure Index Group (cancer ranking)
EPA	Group (cancer ranking) Hazard ranking q_1^* (oral) Reportable Quantity RfD (oral) RfC (inhalation)
NIOSH	Cancer classification
NTP	Cancer classification
Consumer Products Safety Commission (CPSC)	Consumer product limits

STATE
Regulations
and Guidelines:

a. Air: Acceptable Ambient Air Concentrations Guidelines or Standards

b. Water: Water Quality: Human Health

Water Quality: Aquatic Life

Water Quality: Recreational Use

Groundwater Quality Standards

Groundwater Monitoring Parameters

c. Fish and Wildlife Advisories:

Guidance – Chapter 9. References

The intent of this section is to provide interested readers with a list of references concerning the toxicology of the substance and environmental fate and exposure information. List all the references reviewed, whether or not they support the conclusions stated in the document.

Every reference cited in the text, tables, or figures of the profile should appear with an asterisk in the bibliography. Copies of the references must be provided in alphabetical order to the ATSDR and EPA chemical managers and the peer review contractor.

Do not cite secondary sources except when the facts are entirely noncontroversial (as in the case of chemical property values such as molecular weight or boiling point). The inability to find or review a primary reference is not cause for citing the secondary reference. In such a case, the primary source should be referenced "as cited in" the secondary reference. Also, the ATSDR chemical manager must approve any abstract included in the profile.

Guidance for formatting references and the bibliography can be found in the editing guidelines at the beginning of this document.

Include the following new references mentioned in boilerplate sections of **3.7 Susceptibility of Children** and **6.6 Exposures of Children**:

Adinolfi M. 1985. The development of the human blood-CSF-brain barrier. Developmental Medicine and Child Neurology 27:532-537.

Altman PK, and Dittmer DS. 1974. In: Biological Handbooks: Biology Data Book, Volume III, Second Edition. Bethesda, MD, Federation of American Societies for Experimental Biology, 1987-2008, 2041.

Fomon SJ. 1966. Body composition of the infant. Part I: The male reference infant. In: Human Development, Falkner F, ed., Philadelphia, PA, WB Saunders, 239-246.

Fomon SJ, Haschke F, Ziegler EE, and Nelson SE. 1982. Body composition of reference children from birth to age 10 years. American Journal of Clinical Nutrition 35:1169-1175.

Guzelian PS, Henry CJ, Olin SS. 1992. Similarities and Differences Between Children and Adults: Implications for Risk Assessment. Washington, DC, International Life Sciences Institute Press.

Johanson CE. 1980. Permeability and vascularity of the developing brain: cerebellum vs cerebral cortex. Brain Research 190:3-16.

Komori M, Nishio K, Kitada M, Shiramatsu K, Muroya K, Soma M, Hagashima K, and Kamataki T. 1990. FetusBspecific expression of a form of cytochrome P-450 in human liver. Biochemistry 29:4430-4433.

Leeder JS and Kearns GL. 1997. Pharmacogenetics in pediatrics: implications for practice. Pediatric Clinics of North America 44:55-77.

Morselli PL, Franco-Morselli R, and Bossi L. 1980. Clinical pharmacokinetics in newborns and infants. Clinical Pharmacokinetics 5:485-527.

National Research Council (NRC). 1993. Pesticides in the Diets of Infants and Children. Washington D.C., National Academy Press.

Owen GM, and Brozek J. 1966. Influence of age, sex, and nutrition on body composition during childhood and adolescence. In: Falkner F, ed. Human Development. Philadelphia: WB Saunders, 222-238.

Setchell BP and Waites GMH. 1975 The blood testis barrier. Chapter 6. In: Creep RO, Astwood EB, eds.; Geiger SR, executive ed. Handbook of Physiology: Endocrinology V. Washington, DC: American Physiological Society.

Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2E1 in the human liver: hypermethylation control of gene expression during the neonatal period. European Journal of Biochemistry 238:476-483.

West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. Journal of Pediatrics 32a:10-18.

Widdowson EM and Dickerson JWT. 1964. Chapter 17: Chemical Composition of the Body. In: Comar CL and Bronner F, eds. Mineral Metabolism: An Advanced Treatise Volume II The Elements Part A. New York: Academic Press.

Ziegler EE, Edwards BB, Jensen RL, Mahaffey KR, Fomon SJ. 1978. Absorption and retention of lead by infants. Pediatric Research 12:29-34.

Guidance – Chapter 10. Glossary

The standard glossary (Attachment O and Exhibit 27) should be included in every document. Substance-specific recommendations for revisions to the glossary can be made to the chemical manager, who can approve revisions without consulting the guidance committee. Revisions that are not substance-specific (i.e., that might apply to any other profile) should be brought to the attention of the guidance committee.

Guidance –Profile Appendices

APPENDIX A. ATSDR MINIMAL RISK LEVELS

Appendix A consists of a two-page introductory statement and MRL worksheets describing the methodology used and all calculations involved in deriving the MRLs. See Exhibit 14. Separate worksheets should be completed for each MRL that is derived.

APPENDIX B. USER'S GUIDE

See Exhibit 13.

APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

The standard Appendix C (Exhibit 25 and Attachment B) should be included in every document. Substance-specific recommendations for changes, additions, and deletions can be made to the chemical manager, who can approve them without consulting the guidance committee. Changes, additions, or deletions that are not substance-specific (i.e., might apply to any other profile) should be brought to the attention of the guidance committee.

INDEX

The Index (see Exhibit 26) should follow immediately behind Appendix C (or the last appendix if the particular profile required additional appendices). The following terms provide a basic template for the terms to be included in the index. The index should be tailored to fit the profile using chemical-specific terms that may be appropriate for a given profile. Like-wise, terms from the list below that are not relevant for a profile, should be excluded. Chemical-specific terms should be discussed between the principal author and the chemical manager to select the most appropriate terms.

immune system
immunological effects
insects
Integrated Risk Information System
Intermediate-duration
kidney
kidney effects
liver
LOAEL
lung
lung cancer
lymphoreticular effects
milk
Minimal Risk Levels (see MRL)
moss
MRL
Musculoskeletal effects
National Priorities List (see NPL)
neurobehavioral
New Bedford
NIOSH
NOAEL
NOES
NPL
ocean
ocular effects
partition coefficients
PBPD
PBPK
pharmacodynamic
pharmacokinetic
physiologically based pharmacodynamic (see PBPD)
physiologically based pharmacokinetic (see PBPK)
precipitation
Public health
pulmonary fibrosis
RCRA
RDA
reference dose (see RfD)
regulations
renal effects
reportable quantity
Resource Conservation and Recovery Act (see RCRA)
RfD
salmon
sea
sediment
selenium
shrimp
SMR
soil
solubility
Standardized mortality ratio (see SMR)
sulfides
surface water
thyroid
time-weighted average
tomato
toxicokinetic
Toxics Release Inventory (see TRI)
tremors

APPENDICES

ATTACHMENT A. GUIDANCE ON PREPARING THE SUPPLEMENTAL DOCUMENT

The supplemental document should be produced prior to the development of the profiled substance. It consists of two sections: the summary tables for toxicity studies and the summary tables for toxicokinetic studies. Each contains summary information from all studies reviewed for potential inclusion in Chapter 3 of the profile.

The supplemental document is produced using the ATSDR EZ-Tox database. Access to the database is administered by ATSDR. Basic guidance for the content development and appearance follows below.

TITLE PAGE

This should follow the format shown in Exhibits 29 or 30. The word "DRAFT" should remain in the title of all submissions of the supplemental document.

FOREWORD

This should follow the format shown in Exhibit 31.

SECTION TITLE PAGES

The supplemental document is divided into two sections.

- Summary Tables for Toxicity Studies.
- Summary Tables for Toxicokinetic Studies.

A title page for each section within the supplemental document should be included. These should follow the format shown in Exhibit 32 and be placed on the pages preceding the toxicity and toxicokinetics summary tables, respectively.

PAGE NUMBERING AND FOOTER

Page numbers should appear on all pages except the title pages, foreward, and legends.

For all drafts submitted prior to the final submissions, the footer should include the date of submission and should appear 0.7 inches from the bottom of the page on the title page, the foreword, and the section title pages.

*** DRAFT — DO NOT CITE OR QUOTE —[MONTH DAY, YEAR] ***

For the final pre-public-comment and post-public-comment versions, the date should be removed from the footer.

LEGENDS

There are standard legends for both the toxicity and the toxicokinetic summary tables (see Exhibits 33 and 34). Legends should be placed on the page immediately preceding the tables. This legend will explain the abbreviations and codes used within the table. Abbreviations for the tables and legends, which are also the result of the proper use of the worksheets, are shown in Attachment P of this guidance.

It may be necessary to abbreviate terms within descriptions of effects associated with LOAELs. An explanation of these abbreviations should be added to the table legend. If these abbreviations are not substance-specific, they must be added to guidance Attachment P by the guidance committee to insure consistency. Additions to Attachment P should be suggested to the chemical manager. The chemical manager should then inform the guidance committee of the suggestion.

The legends contain abbreviations for common prenatal and postnatal time measurements.

The source of conversion factors should be listed at the bottom of each legend, as follows:

> **Source of Conversion Factors used in the Supplemental Document:** EPA. 1988. Recommendations for and documentation of biological values for use in risk assessment. Cincinnati, OH: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. EPA-60016-87-008.

TABLES

Examples of the summary tables for toxicity studies and toxicokinetic studies are provided in Exhibits 35 and 36. These tables are generated by a computer-driven database EZ-TOX.

For a given study, separate records should be created for toxicity and toxicokinetic effects for each route of exposure. For toxicity effects, separate records should be created for death, systemic, immunological and lymphoreticular, neurological, reproductive, developmental, and cancer effect categories. Systemic effects include respiratory, cardiovascular, gastrointestinal, hematologic, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, body weight, metabolic, and "other" systemic effects. If several systemic effects are observed in a given study, they should be reported in the order indicated above (i.e., respiratory effects then cardiovascular effects). Genotoxicity and *in vitro* studies do not need to be summarized in the supplemental document; they may be included at the author=s discretion.

For the LOAEL parenthetical text, present a summary of the endpoint(s) examined and the *degree* to which it was affected, including percentages or ratios if available. Use succinct but comprehensive descriptions, because this is all the description that will appear in the LSE table. Example (neurological): "Impaired righting reflex and constricted pupils." Be as specific as possible. Example: (increased SGOT and SGPT) rather than (increased enzyme activity). Parentheses should enclose an entry. All relevant study details should be discussed fully in the Description of Study section while all relevant effects should be discussed fully in the Results of Study section.

NOAELs are not appropriate for death, genotoxicity, or cancer entries. NOAELs and LOAELs are not appropriate for *in vitro* entries. In studies for which death, genotoxicity, or cancer were monitored and no effect was observed, an entry should be made under the proper category but the NOAEL and LOAEL fields should be left blank for these entries. The lack of findings should be discussed in the Results of Study section.

The age of the animal should be indicated in the Exposure Duration/Frequency field if exposed at times other than adulthood (e.g., Gd, Ld, or ppd). If doses are administered prenatally, note any effects on the mother. In the LOAEL parenthetical text, effects on maternal animals should be so stated. If the study indicates that there were no maternal effects, discuss this in the Results of Study section, but if the study fails to address the issue, and it seems relevant, this also should be indicated. Health effects on the mother are important to fetal health.

If "other" is used as a systemic category, NOAEL information should only be reported when there is an accompanying LOAEL to indicate the effect. Entries for stand-alone NOAEL data should be left blank but discussed in the Results of Study section.

COMMENT SECTIONS

The comment sections of each summary table should present information, if available, in the following order.

1. **Calculations (if any).** If a conversion is done, its purpose should be readily apparent. Units should be shown, and the name of the conversion factor or a descriptive phrase should be parenthetically inserted, unless the function of the conversion is obvious (such as 5 g to 5,000 mg). Conversion descriptions should *not* be restated for subsequent, identical conversions (in the same record).

2. **Description of Study.** Describe the protocol and procedures of the study in detail. Including the goal of the study here may be a good way to subsequently structure the Results of Study section by determining what effects are most important. Try to include the number and sex of animals, the strain and species, the exposure regimen including dose levels, duration, number of exposures and route of exposure, techniques used, and tissues or activities monitored. Example: Groups of 5 male and 5 female Sprague-Dawley rats were administered 10 or 100 mg/kg/day chloroform in oil once daily via gavage for 5 days. Five rats of each sex served as controls. Liver and kidney weights were measured and SGOT and SGPT activities were followed. Histopathological examination was done on tissues from the liver, kidneys, and lungs.

3. **Results of Study.** Summarize the results of the study and the author's conclusions. Note the most essential results of the study. The Results of Study section should summarize all effects vital to the profile. The following relevant or useful information should be discussed:

Lowest levels at which nonadverse effects were seen (if different from lowest adverse levels)
Gradation of effects
Incidence of effect (for cancer)
Gender or strain difference.

4 **Comments.** If there is any supporting information for the calculations that you feel should be supplied, present this first in the Comments section. Next, discuss the conclusions of the study's authors, *if* they differ from yours. *Suggested* wordings for this discussion are,

"Authors' conclusions: . . ." or "(The authors/Smith et al.) felt that their study (indicated that/supported the) . . . ." If you feel it is helpful, you can discuss authors' conclusions that also involve *other* studies. Indicate when this is the case, but avoid long discussions of other studies. Literature citations may be appropriate. If the other study is already in the References, use the standard citation format (Smith et al. 1988). If not, supply the author name(s), journal information, and year, but not title of the study (as with citations in *Science)*. Conclude with your own evaluation of the study, *if* there are any problems with the study. The intention is to provide a summary of caveats and an indication of any reasons why the study should not be used in the profile.

Considerations of the limitations of a study should include the following: Was a dose-response relationship established? Did the study sufficiently demonstrate a NOAEL or LOAEL? Were appropriate statistical analyses performed and were results statistically significant? Are results biologically significant? Were the data presented accurately (do the numbers in tables and figures add up and agree with the text)? Is the overall quality of the study adequate? Negative answers to any of the above questions, should be noted in this section. Additionally, the adequacy of the description and/or the appropriateness of the following should be considered: purity of test material; vehicle, route of exposure and treatment regimen; any problems with procedures; number of animals used and number of treatment groups; appropriate number and comparability of controls; mortality rate; frequency of observations; and endpoints measured and methods to evaluate endpoints. Note if the study is in agreement or disagreement with the rest of the literature, or if it supports or contradicts any particular study. *Suggested* wordings for this conclusion are, "Limitations: . . ." or "This study (is/appears to be) (somewhat) (deficient/commendable) due to the (lack/inconsistent evaluation/inclusion) of . . . . ." If you wish, you are also welcome to indicate commendable or noteworthy aspects of the study.

If EPA used this study to derive an RfD or RfC for the substance, the value may also be presented in this section.

LSE TABLES AND FIGURES

The LSE tables and figures are generated from the supplemental document database, and the way that studies are entered into the supplemental database determines their representation in the LSE tables and figures.

Proper entry of data in the supplemental tables provides that each study, species, duration, major effect category, and study protocol is represented with a different key number in the LSE tables and figures across major effect categories (i.e., death, systemic, immunological, neurological, reproductive, developmental, and cancer effect categories). See Exhibit 37 for information regarding data entry into the supplemental document.

Please note that within the "systemic" major effect category are subcategories such as respiratory, cardiovascular, gastrointestinal, etc. The same study, species, duration, and study protocol across these subcategories is represented with the same LSE key number.

All NOAELs and LOAELs from the same study, species, duration, and study protocol are represented by the same LSE key numbers.

As a general rule, for a given study all NOAELs and LOAELs should be entered in the tables. One exception is when effect levels are different between males and females; in this case, the more sensitive sex is presented in the LSE figure.

Similarly, the principal author, and chemical manager may choose not to include in the LSE tables certain effects (or entire studies) that appear in the supplemental tables.

MISCELLANEOUS COMMENTS CONCERNING DATA COLLECTION FOR THE SUPPLEMENTAL DOCUMENT

Quality Assurance/Quality Control

Sufficient quality control procedures should be in place to ensure minimal discrepancies in the information extracted from papers and calculations done upon data. Because this is the basis upon which all subsequent statements shall be made, authors should use as much care as is necessary to produce a quality supplemental document. Good project management dictates that this should be accomplished with the first draft of the document.

Significant Figures

Do *not* round numbers until after *all* conversions have taken place. At that point, round value to the same number of significant figures as the datum point, e.g., 0.15 = 0.2 mg/kg/day and 0.25 = 0.3, where the reported dose was 10 ppm in feed.

If more than one experimentally determined datum point enters into the conversion, use the number of significant figures that the datum with the least number of significant figures has. In some cases, authors will want to use more significant figures than are technically called for. A common instance where this might be done is when experimenters report an administered dose as, for example, "5 mg/kg." It is safe to assume that the experimenters actually measured the substance with more precision than the single significant figure stated (i.e., 5.0 mg/kg); it would be a disservice to report the results, after rounding, with one significant figure. In such cases, adding an additional significant figure is advised. Disregard the number of significant figures that are in the conversion factors themselves unless your scientific judgment dictates that the precision of a certain conversion factor is pertinent. Standard scientific practice is to resort to scientific notation in order to present large numbers with unambiguous precision. Nevertheless, scientific notation would be confusing to some lay readers and burdensome for table preparation. Therefore, do not use scientific notation only to retain precision. For example, if 4 were converted to 2,557 round it and present it as 2,600, *not* as 2.6×10^3. Of course, this is *not* to say that scientific notation is never to be used in a profile, nor that authors are banned from using it after a particular conversion if they consider it vital. MRLs are always rounded to 1 significant figure.

"Pulse" or Other Complicated Dosing Regimens

If complicated dosing regimens are used, explain the regimen as fully and succinctly as possible under the "Exposure Duration/Frequency" (ED/F) column. You may need to resort to an inexact, simplified portrayal of the regimen that more fully conveys the effective dose, as opposed to simply listing as many details as space permits and having the rest deleted. Then, explain the regimen fully in the ADescription of Study@ section. Keep in mind that most readers will only see the abbreviated version appearing in the ED/F column of the LSE table, without the benefit of the supplemental document. Therefore, strive to make the ED/F entry as self-sufficient as possible.

ATTACHMENT B: ABBREVIATIONS AND ACRONYMS

ACGIH	=	American Conference of Government Industrial Hygienists
ADME	=	absorption, distribution, metabolism, excretion
AOAC	=	Association of Analytical Chemists
APHA	=	American Public Health Association
ASTM	=	American Society for Testing and Materials
ATSDR	=	Agency for Toxic Substances and Disease Registry
AWQC	=	Ambient Water Quality Criteria
BBDR	=	biologically based dose-response
BCF	=	bioconcentration factor
CEL	=	cancer effect level
CERCLA	=	Comprehensive Environmental Response, Compensation, and Liability Act
CM	=	chemical manager
CMR	=	*Chemical Marketing Reporter*
CPN	=	chronic progressive neuropathy
CPSC	=	Consumer Product Safety Commission
DHHS	=	Department of Health and Human Services
DOC	=	Department of Commerce
ECF	=	extracellular fluid
EEGL	=	emergency exposure guidance level
EPA	=	Environmental Protection Agency
FDA	=	Food and Drug Administration
HDSB	=	Hazardous Substances Data Bank
IARC	=	International Agency for Research on Cancer
IDLH	=	immediately dangerous to life and health
IPCS	=	International Programme for Chemical Safety (part of WHO)
K_m	=	Michaelis-Menten equilibrium constant
LOAEL	=	lowest observed adverse effect level
LSE	=	level of significant exposure
MCLG	=	maximum contaminant level goal
MRL	=	minimal risk level
MTD	=	maximum tolerated dose
NAAQS	=	National Ambient Air Quality Standards
NAPL	=	nonaqueous-phase liquid
NAS	=	National Academy of Science
NFPA	=	National Fire Protection Association
NHANES III	=	Third National Health and Nutrition Evaluation Survey
NIOSH	=	National Institute for Occupational Safety and Health
NKC	=	natural killer cell
NOAA	=	National Oceanic Atmospheric Administration
NOAEL	=	No observed adverse effect level
NOES	=	National Occupational Exposure Survey
NPL	=	National Priorities List
NRC	=	National Research Council

NTP	=	National Toxicology Program
OSHA	=	Occupational Safety and Health Administration
PA	=	principal author
PBPK/PD	=	physiologically based pharmacokinetic/pharmacodynamic (modeling)
PEL	=	permissible exposure limit
PHS	=	Public Health Statement
POTW	=	publicly owned treatment works
PVC	=	polyvinyl chloride
REL	=	recommended exposure limit
RfC	=	reference concentration
RfD	=	reference dose
SAR	=	structure-activity relationship
SMCL	=	secondary maximum contaminant level
SNARL	=	suggested no-adverse-response level
SPEGL	=	short-term public emergency guidance level
STEL	=	short-term exposure limit
TLV	=	threshold limit value
TRI	=	Toxics Release Inventory
TWA	=	time-weighted average
USDA	=	U.S. Department of Agriculture
USGS	=	U.S. Geological Survey
USITC	=	U.S. International Trade Commission
V_{max}	=	maximum velocity
VOC	=	volatile organic compound
WHO	=	World Health Organization

ATTACHMENT C: EVALUATING THE QUALITY OF A TOXICOLOGICAL STUDY

I. Test material

1. Was it purchased or synthesized in-house?

2. Was the same lot used for all experiments?

3. Were any impurities present?

   If so, were the impurities removed?

4. Is the test material stable under experimental conditions?

   If not, were any adjustments made?

5. Was a vehicle used for administration?

6. Were the doses reported in the study?

II. Animal selection

1. What is the rationale for the species selection?

2. Were the animals disease-free?

3. Is the model appropriate for the end-point effects studied?

4. Optimal criteria at specific intervals:

	Acute	**Intermediate**	**Chronic**
Number of treatment groups	3-4	3	3
Number of animal groups	6-10	10-20	50/sex/treatment
Age of animals	>6 weeks	Young adult	Young adult
Control groups	Required	Required	Required

5. Are the species, strain, sex, age, treatment schedule, and vehicle the same for control as for treated animals?

III. Study design

1. Are the route(s) expected for human exposures or other (inhalation, oral [diet, drinking water gavage, other], dermal [intact, abraded, occluded])?

2. Is the exposure regimen daily, continuous, or intermittent (e.g., 6 h/d, 5 d/wk)?

3. Is the mortality loss for a chronic study no more than 5-10%?

4. Optimal criteria at specific intervals:

	Acute	**Intermediate**	**Chronic**
Dose Selection	At least 3	Not specified	2 (MTD and LOAEL from a 90-d dose screen)
Period of exposure	Up to 14 d	15-364 d	365 or more
Period of observation	14 d	Every 12-24 hr	Every 24 hr
Body weight measured	Weekly	Weekly	Weekly up to 13; then every 2 wk

IV. End point effects

1. Were appropriate methods used to measure end-point effects?

2. Were these methods state-of-the-art?

3. Was a dose-response relationship established?

4. Did the study sufficiently demonstrate a NOAEL or LOAEL?

5. Were appropriate statistical analyses performed?

6. Were the results statistically significant (at least $p<0.05$)?

7. Optimal criteria at specific intervals:

	Acute	Intermediate	Chronic
Organ weights recorded	Not specified	Liver, kidney, brain, gonads, heart, etc.	Liver, kidney, brain, adrenal, gonads, spleen, lung, etc.
Histopathological gross examination	Gross necropsy	Necropsy and histopathology for liver, kidney, heart, gross lesions, target organs	All tissue in at least control and highest dose group

ATTACHMENT D: EVALUATING THE QUALITY OF AN EPIDEMIOLOGICAL STUDY

V. Overall criteria

1. The study has been published or peer reviewed.

2. The paper should provide:

   A. Background (i.e., supporting rationale, definition, and explanation of the problem).

   B. Study objectives and study design, including assumptions, limitations, and statement of purpose or hypothesis.

   C. Study population and control group (i.e., method of selection, rationale and criteria for inclusion/exclusion, appropriateness and limitations of control group).

   D. Data collection method, including direction and possible magnitude of any bias introduced into the study (i.e., may be single-, double-, or triple-blind to prevent bias). QA, QC, or calibration data are presented for the data collection instrument (method).

   E. Type and length of follow-up.

   F. Account for (via matching, stratification, multivariate analysis, etc.) and clearly define major confounding factors.

   G. Procedures and statistical methods used for data analysis. Significance levels need to display a strong association ($p<0.05$) to rule out the probability of the results occurring by chance variation.

   H. Results that are related to the objectives of the study. Do the numbers in the tables add up?

   I. Discussion of limitations and biases that may have affected the results. The examination of causality (conclusion) should be supported by the results.

   J. A logical, temporal sequence of exposure-response that is toxicologically plausible.

   K. A demonstrated dose-response relationship using valid estimates of exposure and dose.

VI. Types of epidemiological studies

1. Observational studies

A. General points

a. These studies are rarely designed to provide quantitative risk information.

b. Groups are already divided on the basis of some experience or exposure (not created experimentally).

c. Sample size (N) should consider the size of the difference being detected (i.e., rare or common).

d. Small N does not mean study should not be done, rather it might indicate that nothing could be found in the population. The study may need to state that numbers were too few to detect an excess risk.

B. Main types

a. Retrospective (case-control)

(1) These studies are helpful for monitoring substance/drug exposure.

(2) A positive association is demonstrated between the exposure and the disease/effect if the diseased group is more likely to be exposed than the group not diagnosed with the disease/effect. Researcher looks historically to determine exposure after the disease/effect has been determined.

(3) Cases:

(a) The study group must be delineated precisely, not generalized (e.g., premenopausal women and lobular breast cancer).

(b) Optimally, the study should use newly diagnosed cases with specified characteristics during a specified period in a defined population. Deceased cases as well as those alive when study is undertaken should be included.

(4) Controls:

(a) Controls should be representative of the general population in terms of probability and opportunity for exposure, and should represent the population from which cases arose.

(b) Individual matching is optimal.

(5) Advantages:

(a) The number of subjects can be small because the study is initiated by the identification of cases.

(b) More than one risk factor in the same set of data can be identified.

(c) Studies can take into consideration changes in exposure.

(6) Disadvantages:

(a) Information on past events may be inaccurately recorded or not available.

(b) Information supplied by an informant may be consciously or unconsciously biased.

(c) The study yields only an odds ratio that is an estimate of relative risk (i.e., a comparison of incidence for exposed versus unexposed populations). It is advisable to select more than one control group.

b. Prospective (cohort or longitudinal)

(1) Cohort is free of disease/effect but varies in exposure to the supposed factor. The exposed group is then followed to see if the disease/effect develops. The assumption is that exposed individuals are representative of all exposed persons regarding the risk of disease/effect development.

(2) A positive association is demonstrated between the exposure and the disease/effect if the exposed group develops the disease/effect at a greater rate than those not exposed.

(3) Cohort needs to be as similar as possible to the group it is intended to represent.

(4) Advantages:

(a) Permits calculation of incidence rates among exposed and not exposed. Incidence = number of new cases/total population at risk.

(b) Permits observation of many outcomes.

(5) Disadvantages:

(a) Long-term follow-up may be difficult.

(b) Large cohort (study group) is expensive.

c. Historical prospective

(1) Combines advantages of retrospective and prospective

(2) Follows historically identified healthy exposed and unexposed cohorts for the development of disease/effect.

(3) Can calculate actual incidence and relative risk.

d. Cross sectional (prevalence): Both risk factors and disease are determined at the same time (e.g., prevalence of CHD and serum cholesterol level).

2.Experimental studies: General points

A. The impact of varying some controlled factor is studied.

B. These studies are not common, for obvious reasons.

C. Subjects should be divided into treatment groups by random allocation.

3.Occupational studies

A. Ecological

a. Generate hypotheses.

b. A group rather than individual is the unit of comparison.

B. Cross sectional (prevalence)

a. Observations of a group are made at one point in time, yielding prevalence rates. Prevalence = number of old and new cases/total population at risk.

b. These studies represent one of the most frequently used ways of identifying a disease/effect in a community (survey, screening).

c. Cases of short duration are less likely to be found than cases of long duration.

d. These studies are especially suited for subtle, subclinical health effects for which records are unlikely to exist.

e. The relationship between effects and time cannot readily be explored.

C. Case control

a. These studies are used when the disease/effect of interest is relatively rare and would require a large cohort for follow-up.

b. Environmental concentrations and biological levels are often measured.

c. Several occupations or substances may be associated with the disease/effect of interest.

d. The influence of various modifiers can be studied (synergism).

e. Previous jobs are often of greater relevance than current, therefore entire work history needs examination.

D. Cohort

a. Occupational cohort studies are usually mortality studies.

b. Cohort should be defined as broadly as possible, prevalence or incidence.

c. Eliminating workers from the cohort who are not active can lead to serious biases in assessing mortality because this can distort the age distribution of the cohort and omit workers who left because of ill health.

d. Dose-response relationships or high-risk jobs are searched for by dividing cohort into exposure level groups.

ATTACHMENT E: PHS TERMS

The following words and phrases have been used in the PHS of several toxicological profiles. Because these words may be too complex for the intended audience of the PHS, alternative wordings are provided below in an attempt to standardize the language that ATSDR chemical managers use. These terms or other "complex" terms that must be used in the PHS to clarify meaning should be defined in context.

Absorbed: passed into the body through skin, lungs, or stomach

ambient: surrounding

analgesic: (noun) substance designed to reduce pain; (adjective) reduces pain

analysis: examination

analytic: related to examining or investigating; usually describes method

aquatic: found in the water; lives in the water

chemical intermediate: substance used to form other compounds

commodity: substance or product having commercial value

conclude: determine; decide; find out

consumable commodity: substance or product that can be eaten or drunk

consuming: eating; drinking

contagious: spread easily (as a disease) from person to person, animal to animal, or animal to person

correlation: connection between; association between

decomposed: changed to a simpler form, usually in soil

degradation: breakdown

eliminated: removed from the body

emission: release to the environment, including soil, water, or air

ether-like odor: sharp odor

equivocal: uncertain value or worth

excreted: left the body as waste

extractant: substance that separates other substances that are present in a mixture

experimental: tried; done in a scientific laboratory

formulated: created

formulating: manufacturing

inadvertently: not on purpose; accidentally

in conjunction with: along with; at the same time as

incremental: in small amounts (as increase or decrease)

indicate: suggest; show

inflammable: same as flammable

ingestion: swallowing

inhalation: breathing in

is a function of: is affected by; is controlled by (e.g., the long-term toxicity of "X" is a function of dose)

isomer: different form of the same chemical

malignant: causes harm to the body; often cancerous

median concentration: when all concentrations measured are listed in increasing or decreasing order, the concentration that falls in the middle of the list

metabolite: substance created when something is changed in the body, soil, or water

metabolized: changed the form or chemical structure of

nonflammable: will not burn

offspring: newborn animals or humans

permissible: allowable

prostration: inability to stand

qualitative: what kind of; usually describes a test to determine what substance(s) are present

quantity: amount

refrigerant: substance used to lower temperature; coolant

regeneration: comes back in same or different form

resembling odor of chloroform: sweet odor

residue: small amount of a substance that is present or left in the body, soil, water, or air

retardant: something that slows down or prevents

slimicide: substance that kills or prevents pests that make slime and mucus

soil fumigant: substance in smoke or vapor form that kills soil pests

solvent: substance used to dissolve other substances; often a liquid

susceptible: especially vulnerable to

technique: method

therapeutic: designed to improve health

tolerating: withstanding exposure to a substance without experiencing the expected harmful result

toxic: harmful to humans (or animals)

volatile: evaporates easily

Attachment F: Some Hotlines and Other Information Sources from which fact sheets and other risk communication information can be requested to provide ideas [not as primary source material!] for 1.7 How Can Families Reduce the Risk of Exposure to [Chemical X]?

ATSDR
http://www.atsdr.cdc.gov/
See Alerts and Health Advisories, etc.

CDC
http://www.cdc.gov/

National Center for Environmental Health
http://www.cdc.gov/nceh/ncehhome.htm

CDC Prevention Guidelines Database
http://aepo-xdv-www.epo.cdc.gov/wonder/PrevGuid/PrevGuid.htm

Consumer Product Safety Commission
Hotline, 1-800-638-2772
www.cpsc.gov

Duke Occupational and Environmental Medicine
http://gilligan.mc.duke.edu/oem/default.htm
(in particular, the archives of OEM sometimes have interesting information)

EPA
http://www.epa.gov/

Fish and Wildlife Advisories:
http://www.epa.gov/OST/fishadvice/

Air Risk Information Center Hotline (Air RISC): 1-919-541-0888;
http://www.epa.gov/earth100/records/a00119.html

Asbestos Abatement/Management Ombudsman: 1-800-368-5888;
http://www.epa.gov/earth100/records/a00193.html

Emergency Planning and Community Right-To-Know Act (EPCRA) hotline: (description)
1-800-424-9346;
http://epa.gov/epa/epaoswer/hotline/lotintro.htm#epcra

Environmental Justice Hotline: 1-800-962-6215;
http://es.epa.gov/oeca/oej.html

Hazardous Waste Ombudsman: 1-800-262-7937;
http://www.epa.gov/epaoswer/hotline/contacts.htm#ombuds

Indoor Air Quality Information Clearinghouse (IAQINFO): 1-800-438-4318
http://www.epa.gov/iaq

National Lead Information Center Hotline:1-800-532-3394;
http://www.epa.gov/opptintr/lead/nlic.htm;
email: leadctr@epamail.epa.gov

National Pesticide Telecommunications Network: 1-800-858-7378;
http://ace.ace.orst.edu/info/nptn/

National Radon Information Hotline: 1-800-767-7236;
http://www.epa.gov/iaq/radon/rnxlines.html

National Response Center Hotline: 1-800-424-8802 (Spills and Emergencies)
http://www.nrc.uscg.mil

Oil Spill Program Information Line: 1-202-260-2342: email: oilinfo@epamail.epa.gov
http://www.epa.gov/oerrpage/superfnd/web/oerr/er/oilspill/contacts.htm

Resource Conservation and Recovery Act/Underground Storage Tank (RCRA/UST),
Superfund and RCRA Hotline: 1-800-424-9346;
http://www.epa.gov/epaoswer/hotline/index.htm

Safe Drinking Water Hotline: 1-800-426-4791; email: hotline-sdwa@epamail.epa.gov;
http://www.epa.gov/OGWDW/index.html

Toxics Release Inventory - User Support Service:202-260-1531;
http://www.epa.gov/opptintr or http://www.epa.gov/earth100/records/a00249.html

Toxic Substances Control Act (TSCA) Assistance Information Service (TAIS): 1-202-554-1404
email: tsca-hotline@epamail.epa.gov
http://www.epa.gov/earth100/records/a00266.html

FDA
Main FDA Address and Phone Number (for general inquiries):
U.S. Food and Drug Administration (HFE-88) Rockville, MD 20857
Phone: 1-800-532-4440 (in the Washington, D.C., area, please call 301-827-4420)
Fax: 301-443-9767
E-mail: execsec@oc.fda.gov

http://www.fda.gov/opacom/catalog/getinfo.html

FDA Food Information & Seafood Hotline: 1-800-332-4010 (or 202-205-4314 in the DC Area)
http://vm.cfsan.fda.gov/~lrd/hotline.html

NIEHS
800-643-4794 or 919- 541-1919
http://niehs.nih.gov
(source of a number of fact sheets)

NIOSH
800-356-4674
http://www.cdc.gov/niosh/homepage.html

OSHA
Office of Information and Consumer Affairs, (202) 219-8151; http://www.osha.gov/

U.S. Government (general)
http://www.healthfinder.gov/

ATTACHMENT G: INTERPRETING RENAL PATHOLOGY IN THE MALE RAT

Risk assessment approaches generally assume that chemicals producing toxicity and neoplasia in laboratory animals pose similar hazards to humans. For most chemicals, this extrapolation remains appropriate. However, a growing body of evidence indicates that certain chemicals cause nephropathy and renal neoplasia through a mechanism that occurs in male rats but not in humans (or female rats, mice, or other species).

ALPHA$_{2u}$-GLOBULIN INDUCED RENAL PATHOLOGY IN MALE RATS

Numerous investigations have demonstrated a consistent association between the accumulation of hyaline droplets containing alpha$_2$-microglobulin (α_{2u}-g) and certain lesions in the male rat kidney (Borghoff et al. 1991; EPA 1991; Hard et al. 1993; Swenberg et al. 1989). These renal lesions have not been identified in female rats, in mice, or in other laboratory species tested. A number of chemicals (e.g., unleaded gasoline) are capable of inducing accumulation of α_{2u}-g, a low molecular weight protein, in the male rat kidney. The accumulation of this protein (which is synthesized in the liver) initiates a sequence of events that results in protein droplet nephropathy and eventually renal tumors. Exposure of male rats to chemicals inducing alpha$_{2\mu}$-globulin accumulation (CIGA) results in the following histopathological sequence of renal lesions (EPA 1991).

- An excessive accumulation of hyaline droplets containing α_{2u}-g in renal proximal tubules.
- Subsequent cytotoxicity and single-cell necrosis of the tubule epithelium.
- Sustained regenerative tubule cell proliferation, if exposure continues.
- Development of intraluminal granular casts from sloughed cell debris, along with tubule dilation and papillary mineralization.
- Foci of tubule hyperplasia in the convoluted proximal tubules.
- Renal tubule tumors.

Biochemical studies show that CIGA or their metabolites bind specifically, but reversibly, to male rat α_{2u}-g. The resulting α_{2u}-g-CIGA complex appears to be more resistant to hydrolytic degradation by lysosomal enzymes than native, unbound α_{2u}-g. Inhibition of the catabolism of α_{2u}-g, a protein only slowly hydrolyzed by renal lysosomal enzymes under normal physiological conditions, provides a possible basis for the initial stage of protein overload in the nephropathy sequence (EPA 1991; Hard et al. 1993). It has been hypothesized that the sustained protein overload results in single-cell necrosis in the tubule epithelium and increased cell regeneration (a reparative process). The increased proliferative response caused by chemically induced cytotoxicity may be a plausible reason for the development of renal tumors in male rats.

EPA has established three criteria for determining that renal lesions in male rats are caused by α_{2u}-g accumulation; a positive response in each criterion is required. These criteria are:

1) The number and size of hyalin droplets in renal proximal tubule cells of treated male rats have increased.

   The abnormal accumulation of hyaline droplets in the P2 segment of the renal tubule is necessary to attribute the renal tumors to the α_{2u}-g sequence of events. This finding helps differentiate α_{2u}-g inducers from chemicals that produce renal tubule tumors through other mechanisms.

2) The accumulated protein in the hyaline droplets must be α_{2u}-g.

   Hyaline droplet accumulation is a nonspecific response to protein overload in the renal tubule and may not be due to α_{2u}-g. Therefore, it is necessary to demonstrate, normally by immunohistochemistry, that α_{2u}-g accounts for the hyaline droplet accumulation found in the male rat.

3) Additional aspects of the pathological sequence of lesions associated with α_{2u}-g nephropathy must be demonstrated.

   Typical lesions include single-cell necrosis, sloughing of epithelial cells into the proximal tubular lumen, formation of granular casts, linear mineralization of the papilla, and tubule hyperplasia and regeneration. If the response is mild, all of these lesions may not be observed; however, some elements consistent with the pathological sequence must be present.

It should not be expected that a compound that induces α_{2u}-g accumulation will always be found to induce renal tubule tumor formation in the male rat. The ability to detect renal tumors

depends on many features that may not be present in any individual experiment (e.g., sufficient dose to induce effect without early deaths of the animals, insufficient length of exposure or follow-up and incomplete histopathology).

Nephropathy and renal tumors associated with CIGA appear to be unique responses of the male rat. Therefore:

- Nephropathy in the male rat that is associated with α_{2u}-g accumulation should not be used as an endpoint for quantitative noncarcinogenic risk assessment (MRL derivation).
- Renal tubule tumors in the male rat that are associated with α_{2u}-g accumulation should not be used to support qualitative weight of evidence that a chemical poses a cancer risk in humans; these endpoints also should not be used for dose-response extrapolations that estimate human cancer risk.

Kidney effects data related to α_{2u}-g accumulation in the male rat should be discussed in the profile and included in the LSE tables, even though it may not be used for MRL derivation. However, in these cases the association of renal lesions to α_{2u}-g accumulation and the relevance of these endpoints to risk assessment (human extrapolation) should be clearly discussed.

CHRONIC PROGRESSIVE NEPHROPATHY (CPN)

Another factor to consider in using rat kidney effects for risk assessment is the species-related condition CPN. CPN is an age-related spontaneous disorder of rats that is more severe in males than in females, and that affects certain strains more than others. CPN is more common in Sprague-Dawley and F344 rats than in the Wistar strain (Gray 1986), and it is also common in the Osborne-Mendel rat (Goodman et al. 1980). The etiology of CPN is not known, but the severity of this condition may be influenced by a number of factors, particularly dietary manipulation affecting protein content or caloric intake (Masoro and Yu 1989). If their lifespan is long enough, most rats will have this renal lesion to some degree at the time of death.

Chronic administration of CIGA to male rats may result in exacerbation of CPN, characterized by increased severity and earlier onset of the disease. However, chemicals that do not induce α_{2u}-g accumulation may cause damage by direct nephrotoxicity or may cause damage indirectly by accelerating the onset and increasing the severity of CPN. Histopathologic characteristics of CPN (EPA 1991; UAREP 1983) include some lesions that are also found in α_{2u}-g nephropathy, as well as lesions that are distinctive. Single-cell necrosis, regenerating tubules, and focal hyperplasia of proximal tubule epithelium are common to CPN and to α_{2u}-g nephropathy. CPN lesions that are *not* components of α_{2u}-g nephropathy include prominent thickening of tubules and glomerular basement membranes, hyaline casts consisting of homogenous, proteinaceous material (distinct from granular casts containing cellular debris), interstitial mononuclear cell infiltration, fibrosis, tubule atrophy, and sclerotic glomeruli. In advanced cases of CPN, sporadic tubules may contain excessive numbers of hyaline droplets similar in appearance to those induced by CIGA. However, these droplets do not show immunochemical evidence of α_{2u}-g (Hard et al. 1993).

CPN in the aging male rat can complicate the interpretation of other renal lesions. However, nephropathy in the male rat that is not attributable to either CPN or α_{2u}-g accumulation may provide endpoints that are suitable for consideration in the risk assessment process, particularly if similar effects are seen in female rats, in mice, or in other species. Generally, lesions of CPN in exposed rats should be excluded as endpoints used in quantitative risk assessment (MRL derivation). However, there may be an exception to this guideline in a few cases. Lesions of CPN in exposed rats may be considered potential endpoints for estimating noncarcinogenic risk if exposed male and female, or only female[*], rats have lesions of CPN that exhibit a clearly defined dose response. More specifically, with increasing exposure doses there should be a progressive significance of CPN lesions as characterized by (a) an earlier age of onset, (b) increasing severity, (c) an increased frequency of animals affected (one or any combination of these three items may be present). Observation of renal effects in other similarly exposed species contributes to the weight of evidence in these cases.

[*]In untreated rats, CPN is typically much more severe in males. If exposed females exhibit a dose-response, such a pattern may be obscured in the exposed male rat due to the severity of the lesion.

In cases where the above criteria are met, NOAEL values for lesions of CPN can be considered for quantitative risk assessment. A NOAEL in this situation is defined as a test dose that produces no statistically significant enhancement of CPN lesions compared with the controls. The effect description for NOAEL values should read "no enhancement of CPN in females" (and males, if appropriate). At those doses where enhancement of CPN lesions is observed, effects should be classified as less serious LOAELs or serious LOAELs, depending upon their magnitude. Less serious LOAEL values can be considered for MRL derivation if NOAELs have not been identified. The effect description for LOAEL endpoints should read "dose-related enhancement of CPN in females" (and males, if appropriate).

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ATTACHMENT H: ASSESSING CHOLINESTERASE ACTIVITY INHIBITION

Organophosphorus (OP) and carbamate compounds share a common pathophysiologyCthey combine with and thereby inhibit cholinesterase enzymes, of which acetylcholinesterase in nerve tissue is the most important. Inactivation of acetylcholinesterase results in accumulation of acetylcholine at synapses and neuromuscular junctions. Exposure to OP (e.g., disulfoton, malathion) or carbamate (e.g., baygon, carbaryl) compounds produces a broad spectrum of clinical effects indicative of massive overstimulation of the cholinergic system, including muscarinic effects (parasympathetic), nicotinic effects (sympathetic and motor), and central nervous system effects (ATSDR 1993; Gallo and Lawryk 1991; Kaloyanova and El Batawi 1991). These effects present clinically as symptoms of headaches, weakness, dizziness, blurred vision, psychosis, respiratory difficulty, paralysis, convulsions, and coma. Other typical findings include increased salivation, lacrimation, urination, and defecation. In the following discussion, OP compounds will be used as the prototype-cholinesterase inhibiting toxin.

In principle, cholinesterase activity correlates with the amount of OP compound absorbed in the organism. Therefore, cholinesterase activity is a specific test for exposure to OP compounds (Morgan 1989). There are two principal human cholinesterases, acetylcholinesterase and pseudocholinesterase. Acetylcholinesterase, also referred to as true cholinesterase or erythrocyte acetyl cholinesterase, is found mainly in nervous tissue and erythrocytes, as well as in lymphocytes (Goldfrank et al. 1990). Pseudocholinesterase is often referred to as plasma cholinesterase or serum cholinesterase. Pseudocholinesterase and lymphocyte acetylcholinesterase activities are depressed before erythrocyte cholinesterase activity, suggesting that these cholinesterases are more sensitive indicators of exposure to OP compounds (Fitzgerald and Costa 1993; Iyaniwura 1991; Sundlof et al. 1984). However, erythrocyte cholinesterase recovers more slowly (90B120 days) than pseudocholinesterase or lymphocyte acetylcholinesterase (days to weeks), and is therefore a better indicator after exposure ceases. Depression of pseudocholinesterase activity only indicates possible exposure to OP compounds, whereas depression of erythrocyte and lymphocyte acetylcholinesterases not only indicates exposure but also a neurologic effect, as they reflect inhibition of brain acetylcholinesterase activity. The toxicologic effects of OP compounds are almost entirely due to the inhibition of

acetylcholinesterase in the nervous system. Thus, the toxicity of OP compounds is most appropriately assessed in the laboratory by measurement of the erythrocyte (true) cholinesterase rather than the plasma (pseudo-) cholinesterase. Inhibition of plasma cholinesterase has not been associated with toxicity.

For the purpose of health effect assessment associated with OP compound exposure, the laboratory parameter to be used in profiles is measurement of acetylcholinesterase activity (in erythrocytes and/or the brain). If the rate of acetylcholinesterase inhibition is rapid, the correlation between enzyme inhibition and the severity of clinical symptoms tends to be good. When the rate of acetylcholinesterase inhibition is slow, the correlation may be low or nonexistent. This may happen during long-term occupational OP compound exposure, because the body adapts to the high levels of acetylcholine accumulated in the synapses and neuromuscular junctions (Kaloyanova and El Batawi 1991). Chronic moderate OP compound exposure results in cumulative inhibition of acetylcholinesterase activity. The appearance of symptoms depends more on the rate of fall in acetylcholinesterase activity than on the absolute level of activity reached. Some workers may exhibit 70-80% inhibition of acetylcholinesterase activity after several weeks of moderate exposure without manifesting cholinergic symptoms. Other individuals may develop symptoms at first exposure, even though the inhibition of acetylcholinesterase activity is less than 30%.

In classifying the neurological health effect endpoint of "inhibition of acetylcholinesterase activity" (in erythrocytes and/or the brain), the following guidelines should be followed. A 20-59% inhibition of enzyme activity is classified as a less serious LOAEL; enzyme activity inhibition of 60% or greater is classified as a serious LOAEL. However, in addition to the aforementioned guidelines, consideration should be given to associated clinical symptoms (see Table 3-15b in the guidance for chapter 3). If clinical effects observed at a particular exposure level are most consistent with those symptoms described in the table under moderate or severe poisoning, this exposure level should be classified as a serious LOAEL, even if the degree of inhibition of acetylcholinesterase activity is less than 60%. In those cases where inhibition of enzyme activity of less than 60% is classified as a "serious" LOAEL, the specific clinical effects that lead to this classification (as well as the percentage of enzyme inhibition) should be clearly

stated in the text of Chapter 3 and in the LSE tables. Inhibition of acetylcholinesterase activity of 60% or greater should always be classified as a serious effect. Clinical signs, if present, should be discussed in Chapter 3 and listed in the LSE table entry. In cases where erythrocyte or brain acetylcholinesterase is inhibited by less than 20% (NOAEL) and statistically significant decreases in plasma cholinesterase are observed, this fact should be stated in Chapter 3. This information is useful in quantitative risk assessment since it proves that significant absorption occurred.

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Attachment I: Age at weaning and sexual maturity for common laboratory species and humans.

Species	Age at weaning	Age at sexual maturity (puberty)
Mouse	21 days	50 days
Rat	21 days	56 days
Dog (Beagle)	42 days	240 days
Cat	49 days	240 days
Guinea pig	14 days	70 days
Hamster	21 days	60 days
Rabbit (New Zealand)	56 days	195 days
Gerbil	21 days	70 days
Monkey (Rhesus)	130 days	1825 days
Pig	14-35 days[+]	150 days
Mink	56 days	300 days
Human[a]	6 months - 2 years	13 years (female) 15 years (male)

*Source: EPA. 1988. *Recommendations for and Documentation of Biological Values for Use in Risk Assessment.* Environmental Criteria and Assessment Office, Office of Research and Development, Cincinnati, OH. EPA/600/6-87-008.
+Source: Dr. G. Gomez. North Carolina State University, Veterinary School. Personal communication, April 8, 1998. Commercial operations often begin the weaning process at 2 weeks. At 5 weeks, the sow begins a drastic reduction in milk production.
[a]Age of weaning is age at which breast feeding or formula is stopped by mother or child. Some toddlers are breastBfed longer than 2 years, and some infants are given a steady diet of solid foods before 6 months, though the latter is not recommended.

Attachment J: Historical background rates for various developmental outcomes used in interpreting National Toxicology Program (NTP) developmental studies on rabbits, rats, and mice. Appendices from Research Triangle Institute (RTI) contracted studies, used with permission of NTP. [Tables]

Attachment K: Example of Chapter 3.4 - HEALTH EFFECTS IN WILDLIFE POTENTIALLY RELEVANT TO HUMAN HEALTH (Toxicological Profile for DDT, DDD, and DDE - 2002)

3.4 HEALTH EFFECTS IN WILDLIFE POTENTIALLY RELEVANT TO HUMAN HEALTH

The 1972 EPA decision to ban DDT for most uses in the United States was significantly influenced by a large body of scientific information documenting adverse effects to wildlife (EPA 1975). These observed effects were severe, including the lethality of DDT to birds and fish and the DDE-induced reproductive effects in birds, particularly eggshell thinning (EPA 1975). Although it is difficult to draw firm conclusions about adverse effects to human health based on those observed in wildlife, it is impossible to ignore that the documented effects to wildlife have motivated the investigation of human health effects. It is reasonable to assume that the adverse effects observed in wildlife may also be a concern to humans and that wildlife are possible "sentinels" for human health (NRC 1991). In order to completely address potential concerns for human health, it is necessary to review and evaluate the observed effects of DDT/DDE/DDD to terrestrial wildlife. Exposures for wildlife to DDT and its metabolites in the natural environment are primarily associated with the accumulation and persistence of these contaminants in both aquatic and terrestrial food chains. Ingestion of contaminated food results in the deposition of DDT/DDE/DDD in tissues with subsequent reproductive, developmental, and neurological effects. The most important reproductive effect observed in wildlife concerns eggshell thinning in birds. These and other effects on terrestrial wildlife are discussed in greater detail in Appendix D with the purpose of providing a qualitative synopsis of effects in terrestrial wildlife to address potential concerns that these effects from DDT/DDE/DDD exposure may also occur in humans.

Eggshell Thinning in Birds. Eggshell thinning in birds reached widespread public awareness in the 1960s and 1970s largely because of field observations in wild raptor populations including the bald eagle, peregrine falcon, and osprey, and the association of these effects with abrupt population declines. Experimental studies established a scientific link between DDT/DDE/DDD exposure, particularly DDE, and avian eggshell thinning, which weighed significantly in the decision to ban most domestic crop uses of DDT in the 1970s (EPA 1975). In general, raptors, waterfowl, passerines, and nonpasserine ground birds were more susceptible to eggshell thinning than domestic fowl and other gallinaceous birds, and DDE appears to have been a more potent inducer of eggshell thinning than DDT (Cooke 1973b; EPA 1975; Lundholm 1997; WHO 1989). Further, reproductive disturbances associated with DDT/DDE/DDD exposure continue to be reported in North American populations of predatory birds and/or birds that migrate to regions such as South America where DDT is still used (Lundholm 1997).

Numerous experimental studies have shown that dietary exposures to DDT/DDE/DDD are associated with eggshell thinning and breakage in wild birds including the barn owl (*Tyto alba*) (Mendenhall et al. 1983), the American kestrel (Porter and Wiemeyer 1969), the mallard duck (*Anas platyrhynchus*) (Heath et al. 1969; Risebrough and Anderson 1975; Vangilder and Peterle

1980), the black duck (*Anas rubripes*) (Longcore et al. 1971), the Japanese quail (*Coturnix coturnix japonica*) (Kenney et al. 1972), the bobwhite quail (*Colinus virginianus*) (Wilson et al. 1973) and the the Ringed turtle doves (*Streptopelia risoria*) (Haegele and Hudson 1973; Peakall 1970; Peakall et al. 1975). These experimental results have verified that the field observations of eggshell thinning and reductions in wild raptor populations are associated with releases of DDT. Possible mechanisms of eggshell thinning in birds have been extensively studied and reviewed (Cooke 1973b; EPA 1975; Lundholm 1997; Peakall et al. 1975; WHO 1989). The leading hypothesis for DDE-induced thinning involves an inhibition by *p,p*=-DDE (but not by *o,p*=-DDE or DDT or DDD isomers) of prostaglandin synthesis in the shell gland mucosa (Lundholm 1997). Overall, there is still some question as to the primary mechanism and reviewers have suggested that these may differ between bird species or differ with environmental conditions or physiological state for a given species. There is some question, however, as to the relevance of avian eggshell thinning to human health. There is no anatomical or physiological counterpart of the shell gland, a specialized segment of the oviduct, in humans. The shell gland lays down calcite ($CaCO_3$, calcium carbonate) onto the developing avian egg to form the eggshell (EPA 1975). Mechanisms of action that involve a direct action of DDT/DDE/DDD on the shell gland itself probably have no human relevance, but mechanisms of action that involve intermediate effects, such as reduced blood calcium, may have relevance to human health.

Reproductive Effects. Exposure to DDT/DDD/DDE is associated with reproductive toxicity in avian wildlife including embryolethality (Heath et al. 1969; Longcore et al. 1971; Porter and Wiemeyer 1969), decreased egg size and weight (Jefferies 1969; Peakall 1970; Wilson et al. 1973), delayed oviposition after mating (Cecil et al. 1971; Jefferies 1967, 1969; Peakall 1970; Richie and Peterle 1979; Vangilder and Peterle 1980), ovarian effects (Bitman et al. 1968; Gish and Chura 1970; Keith and Mitchell 1993) and testicular effects (Burlington and Lindeman 1950; George and Sunararaj 1995; Gish and Chura 1970; Locke et al. 1966). Several authors have speculated that these effects are associated with DDT-induced hormonal imbalances (Jefferies 1967) such as DDT induced estrogen-like inhibition of FSH and LH secretion by the pituitary inhibiting ovary development.

In most studies, egg production is not affected by DDT/DDD/DDE exposure (Azevedo et al. 1965; Chen et al. 1994; Davison et al. 1976; Davison and Sell 1972; Heath et al. 1969; Jefferies 1969; Longcore et al. 1971; Mendenhall et al. 1983; Porter and Wiemeyer 1969; Risebrough and Anderson 1975; Scott et al. 1975; Shellenberger 1978; Vangilder and Peterle 1980; Wilson et al. 1973). There are, however, a few reported cases of decreased egg production especially in birds with restricted diets (Cecil et al. 1971; Gish and Chura 1970; Haegele and Hudson 1973; Kenney et al. 1972). Egg fertility and hatchability are not consistently affected by DDT/DDD/DDE exposure. Some studies report significantly decreased fertility and hatchability (Porter and Wiemeyer 1969; Vangilder and Peterle 1980; Wilson et al. 1973), while others do not document significant effects (Azevedo et al. 1965; Haegele and Hudson 1973; Jones and Summers 1968; Scott et al. 1975; Shellenberger 1978). When considered collectively, egg production, fertility, and hatchibility were largely unaffected in numerous studies in a variety of bird species. This may be inconsequential to the overall reproductive success of birds since DDT/DDD/DDE exposure is clearly associated with decreased embryonic survival or fledgling success (Keith and Mitchell 1993).

DDT exposure has been shown to be associated with reduced post-hatch survival in avian wildlife. This effect has been observed in laboratory testing with mallards, pheasant, black duck, chicks; Japanese quail and ringed turtle doves (Azevedo et al.1965; Genelly and Rudd 1956; Haegele and Hudson 1973; Heath et al. 1969; Jones and Summers 1968; Keith and Mitchell 1993; Longcore et al. 1971; Porter and Wiemeyer 1969; Shellenberger 1978). The mechanism of DDT-induced reduced survival after oral exposures to DDT or DDE in maternal birds is hypothesized to be associated with increased body burdens of DDT/DDD/DDE in chicks as either a result of direct toxicity to the chick, or a reduction in parental care-giving among treated birds resulting in chick malnutrition and poor survival.

The implications of these observed effects in wildlife to human health is uncertain as the mechanisms of toxicity are not thoroughly understood. The consistency of the observed reproductive effects to avian wildlife and the field observations of effects to birds and reptiles have stimulated the investigation of reproductive effects in mammalian models that are more directly relevant to humans. *In vitro* mechanism of action studies have resulted in the identification of some DDT isomers and metabolites as androgen antagonists and estrogen agonists. There have been a number of intriguing mechanistic studies of DDT isomers and metabolites in fish that relate to reproductive and developmental effects (Das and Thomas 1999; Faulk et al. 1999; Khan and Thomas 1998; Loomis and Thomas 1999; Sperry and Thomas 1999; Thomas 1999). There are some interesting parallels between mammalian wildlife and human health studies. Similar to the associations made between DDT and preterm deliveries in humans (Saxena et al. 1980, 1981; Wassermann et al. 1982), premature births in California sea lions (*Zalophus californianus californianus*) are associated with elevated DDT concentrations (DeLong et al. 1973). However, the effect could not be solely, causally isolated to DDT due to the presence of PCBs.

Developmental Effects. The developmental effects of DDT/DDD/DDE on reptiles and avian wildlife have received considerable attention. Studies of alligator populations at Lake Apopka in Florida, where a pesticide spill occurred in 1980, have reported various reproductive effects including reduced clutch viability (Woodward et al. 1993), altered steroidogenesis (Crain et al. 1997; Guillette et al. 1995), abnormal ovarian morphology and plasma 17β-estradiol levels (Guillette et al. 1994), and reductions of phallus size and serum testosterone (Guillette et al. 1994, 1995, 1996, 1997, 1999). The authors hypothesized that the estrogenicity of DDT and other contaminants induced hormonal imbalance in the alligators, causing the observed effects (Guillette and Crain 1996). The contribution of DDT/DDE/DDD (only one component of the mixture of pesticides present) to the observed effects is uncertain. However, other experimental findings support the hypothesis that certain DDT-related compounds induce estrogenic effects in reptiles which could potentially adversely affect reproduction in a population (*in ovo* DDE exposures in alligators by Matter et al. 1998). In general, reptiles may be particularly susceptible to the endocrine-altering effects of DDT/DDE/DDD, as sex in many species are determined by environmental factors (temperature, etc.,) compared to the genetic sex determining mechanisms in birds and mammals (Crain and Guillette 1998). Organochlorine contaminants in general and *p,p*=-DDE, specifically, are thought to influence sexual dimorphism in the common snapping turtle (*Chelydra serpentina*)(de Solla et al. 1998). Snapping turtles in Ontario, Canada, lacked the normal sexual dimorphism in the distance between cloaca and plastron which was attributed to the antiandrogenic effects of *p,p*=-DDE.

DDT exposure is also associated with developmental abnormalities in amphibians and avian wildlife. DDT exposures are associated with delayed tadpole metamorphosis in the frog (*Rana temporaria*) (Cooke 1972, 1973a) and altered facial features (Cooke 1970a). Developmental effects in avian wildlife associated with exposure to DDT/DDD/DDE include a reduced growth (Seidensticker 1968), decreased ability to thermoregulate (Vangilder and Peterle 1980), behavioral alterations (Heinz 1976), reduced testicular development (Burlington and Lindeman 1952), and development of ovarian tissue and oviducts in genetic males (Fry and Toone 1981). Wildlife species may be appropriate sentinels of developmental effects in humans because certain effects, particularly reduced early survival in young, occurred consistently across several species under various exposure conditions.

Neurological and Behavioral Effects. Neurological effects (tremors, convulsions, hyperactivity, and behavioral changes) were observed in mammalian wildlife, amphibians, and avian wildlife experimentally exposed to DDT or DDE, particularly after administration of lethal doses or after administration of lower doses when food intake was restricted. Tremors were the most commonly reported neurological effect and have been reported in the brown bat (the short-tailed shrew (*Blarina brevicauda*) (Blus 1978), the free-tailed bat (*Tadarida brasiliensis*) (Clark and Kroll 1977) the big brown bat (*Eptesicus fuscus*) (Luckens and Davis 1964) and Pipistrelle bats (Jefferies 1972). Studies generally did not offer explanations as to the possible mechanisms that caused tremors, although it is reasonable to assume a mechanism similar to that seen in laboratory animals. Diets were experimentally restricted in several studies to simulate the health effects of DDT/DDE/DDD mobilized from fat during periods of energetic stress in the wild such as may occur, for example, during periods of nesting, migration, or thermal or other stress. Reviews (EPA 1975; WHO 1989) have postulated that during periods of energy stress, DDT mobilized from fat is redistributed to the brain (presumably because of the high lipid content in brain tissue) where it induces neurological effects and death. A study in bats (Clark and Kroll 1977) demonstrated that DDT residues in the brain increase substantially when the diet was restricted. Although a direct action on the central nervous system in wildlife has not been confirmed by observations of brain lesions, one study documented significant decreases in brain neurotransmitter levels associated with increased brain DDE residue levels after sublethal dietary exposures (Heinz et al. 1980). Alterations in neurotransmitter levels may explain changes in bird behavior that were observed in several species. Neurological effects observed in amphibians exposed to DDT/DDE/DDD in water include uncoordinated movement (Cooke 1970b) and hyperactivity (Cooke 1972, 1973a), tremors, lack of muscular coordination and weakness (Harri et al. 1979). Most available data suggest that wildlife species exhibit neurological effects similar to those observed in humans. These neurological effects, however were observed in wildlife at lethal exposure levels or in energy-stressed animals at lower exposure levels.

In avian wildlife DDT/DDD/DDE exposures are associated with decreased brain dopamine levels with a significant negative correlation observed between neurotransmitter levels and DDE residues in the brain (Heinz et al. 1980). Tremors have also been observed in bald eagles (*Haliaetus leucocephalus*) (Chura and Stewart 1967; Locke et al. 1966), kestrels (*Falco sparverius*) (Porter and Wiemeyer 1972), double-crested cormorants (*Phalacrocorax auritus*) (Greichus and Hannon 1973), pheasants (Azevedo et al. 1965), bobwhite quail (*Colinus virginianus*) (Hill et al. 1971), Japanese quail (Davison et al. 1976; Gish and Chura 1970), house

sparrows *(Passer domesticus)* (Boykins 1967), cardinals (*Richmondena cardinalis*), and blue jays (*Cyanocitta cristata*) (Hill et al. 1971), homing pigeons (*Columba livia)* (Jefferies and French 1971) (Jefferies and French 1972), and domestic chickens (Glick 1974). Balance disturbances have also been observed (in some cases prior to death) in pheasants that (Azevedo et al. 1965), Bobwhite quail (*Colinus virginianus*) (Hill et al. 1971), cardinals (*Richmondena cardinalis*), and blue jays (*Cyanocitta cristata*) (Hill et al. 1971). Neurological effects in avian wildlife are also manifested as behavioral effects. These include the delayed onset of nocturnal restlessness indicative of normal migratory behavior (Mahoney 1975), significantly decreased courting behavior (Haegele and Hudson 1977), and decreased nest attendance by parental birds (Keith and Mitchell 1993).

Other adverse effects observed in wildlife species are described in detail in Appendix D. This section only provides a summary of reproductive, developmental and neurological effects that are the primary adverse effects to terrestrial wildlife associated with DDT/DDD/DDE exposure.

Attachment L: Metabolic enzymes whose expression or activity varies developmentally: Table 2 from Leeder, JS and Kearns, GL. 1997. Pharmacogenetics in Pediatrics: Implications for Practice. Pediatric Clinics of North America 44:55-77.

Table 2. Developmental Patterns for the Ontogeny of Important Drug-Metabolizing Enzymes

Enzyme(s)	Known Developmental Pattern
Phase I Enzymes	
CYP2D6	Low to absent in fetal liver but uniformly present at 1 week of postnatal age. Poor activity (approximately 20% of adult) at 1 month of postnatal age. Adult competence attained by approximately 3B5 years of age.
CYP2C19, CYP2C9	Not apparent in fetal liver. Inferential data using phenytoin disposition as a nonspecific pharmacologic probe suggest low activity in first week of life, with adult activity reached by 6 months of age. Peak activity (as reflected by average values for V_{max}, which are 1.5B1.8-fold adult values) may be reached at 3B4 years of age, which declines to adult values at the conclusion of puberty.
CYP1A2	Not present to an appreciable extent in human fetal liver. Adult levels reached by 4 months and may be exceeded in children 1B2 years of age. Activity slowly declines to adult levels which are attained at the conclusion of puberty. Gender differences in activity are possible during puberty.
CYP3A7	Functional activity in fetus is approximately 30%B75% of adult levels of CYP3A4.
CYP3A4	Low activity in the first month of life, with approach toward adult levels by 6B12 months of postnatal age. Pharmacokinetic data for CYP3A4 substrates suggest that adult activity may be exceeded between 1B4 years of age. Activity then progressively declines, reaching adult levels at the conclusion of puberty.

Attachment M: Alternate Names for Enzymes

Phase II Enzymes

NAT2 Some fetal activity present by 16 weeks. Virtually 100% of infants between birth and 2 months of age exhibit the slow metabolizer phenotype. Adult phenotype distribution reached by 4B6 months of postnatal age, with adult activity present by approximately 1B3 years of age.

TPMT Levels in fetal liver are approximately 30% of those in adult liver. In newborn infants, activity is approximately 50% higher than in adults, with a phenotype distribution that parallels that in adults. In Korean children, adult activity appears at approximately 7B9 years of age.

UGT Ontogeny is isoform specific as reflected by pharmacokinetic data for certain substrates (e.g., acetaminophen or chloramphenicol). In general, adult activity as reflected from pharmacokinetic data seems to be achieved by 6B18 months of age.

ST Ontogeny (based on pharmacokinetic studies) seems to be more rapid than that for UGT; however, it is substrate specific. Activity for some isoforms (e.g., that responsible for acetaminophen metabolism) may exceed adult levels during infancy and early childhood.

CYP, cytochrome P450; NAT2, *N*-acetyltransferase-2; TPMT, thiopurine methyltransferase; UGT, glucuronosyltransferase; ST, sulfotransferase.
Data summarized from information and references presented in the text.

Phase I Enzymes

Standard Name	Alternate Names
CYP1A2	7-ethoxy resorufin o-deethylase EC1 P450d (human, rat) P-448 (rat) LM_4 (rabbit) MC_4 (hamster) Mkah2 (monkey) P-450-D3, P-450-D2, Dah2 (dog) DP-4501A-61 (chicken) P_3, P_2 (mouse)
CYP2C9	(methyl) hydroxylase for several compounds, e.g., tolbutamide, phenytoin, tieneilic acid EC1.14.99

MP-1, MP-2 IIC1. Human-2, mp-4, HM2, pHLS.5, hPA6 (human)

CYP2C19 S-mephenytoin hydroxylase
EC 1.14.13
11a (human)

CYP2D6 Nifedipine oxidase
EC 1.14.99
db1 (human)

CYP3A4 nf-25, hPCN1, nf-10 (human)

CYP3A7 HFLa, HFL33, Hlp2 (human)

Phase II Enzymes

n-acetyltransferase 2 (NAT2)

Acetyltransferase, arylamine
beta.-Naphthylamine N-acetyltransferase
4-Aminobiphenyl N-acetyltransferase
5-HT N-acetyltransferase
Acetyl CoA-arylamine N-acetyltransferase
Acetyltransferase, 2-naphthylamine N-
Acetyltransferase, 4-aminobiphenyl
Acetyltransferase, p-aminosalicylate N-
Acetyltransferase, procainamide N-
Arom. amine N-acetyltransferase
Arylamine acetylase
Arylamine acetyltransferase
Arylamine N-acetyltransferase
Dapsone N-acetylase
Dapsone N-acetyltransferase
E.C. 2.3.1.5
Indoleamine N-acetyltransferase
p-Aminosalicylate N-acetyltransferase

thiopurine s-methyltransferase (PMT)

Methyltransferase, mercaptopurine (9CI) (CA INDEX NAME)
Mercaptopurine methyltransferase
Thiopurine methyltransferase

glucuronosyltransferase (UGT)

Glucuronosyltransferase, uridine diphospho- (9CI) (CA INDEX NAME)

1-Naphthol-UDP-glucuronosyltransferase
4-Hydroxybiphenyl UDP-glucuronosyltransferase
4-Methylumbelliferone UDP-glucuronosyltransferase
4-Nitrophenol UDP-glucuronyltransferase
Ciramadol UDP-glucuronyltransferase
E.C. 2.4.1.17
Glucuronosyltransferase, uridine diphosphoglucuronate-4-hydroxybiphenyl Glucuronyltransferase
Glucuronyltransferase, uridine diphospho-
Nitrophenol UDP-glucuronosyltransferase
p-Hydroxybiphenyl UDP glucuronyltransferase
p-Nitrophenol UDP-glucuronyltransferase
p-Nitrophenylglucuronosyltransferase
p-Phenylphenol glucuronyltransferase
phenol-UDP-glucuronosyltransferase
UDP glucuronosyltransferase
UDP glucuronyltransferase
UDP-glucuronate-4-hydroxybiphenyl glucuronosyltransferase
UDPGA transferase
UDPGA-glucuronyltransferase
Uridine 5'-diphosphoglucuronic acid transferase
Uridine 5'-diphosphoglucuronyltransferase
Uridine diphosphate glucuronyltransferase
Uridine diphosphoglucuronosyltransferase
Uridine diphosphoglucuronyltransferase

sulfotransferase (ST)
3'-Phosphoadenosine 5'-phosphosulfate sulfotransferase
6-Hydroxymethylbenzo[a]pyrene sulfotransferase
PAPS-Sulfotransferase
PAPS-Sulphotransferase
Phosphoadenosine phosphosulfate transferase
S-Sulfotransferase

Sources:
P450 enzymes

Medline citations

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Phase II enzymes:
Chemical Abstracts, as searched on February 17, 1998.

ATTACHMENT N: DEVELOPING ADEQUACY OF THE DATABASE SECTION

Adequacy of the database sections are found in Chapters 3, 6, and 7. Under each of the sections entitled "Adequacy of the Database," ATSDR has supplied boilerplate as follows.

> **Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of [substance x] is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of [substance x].**
>
> **The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.**

"NTP" should be used the second and third time the boilerplate is included in the profile. It is only necessary to define NTP when first used in the profile.

GENERAL GUIDANCE

The categories of data needs to be discussed within each chapter are indicated in the Outline for Toxicological Profiles (Exhibit 1). These subheadings should be identified without assigning section numbers. They should be indented, bold, and followed by a period, two spaces, and then text.

The text that accompanies each data need should be a synthesis of existing data. References should be cited. The word "adequate" should not be used when discussing data needs. The text should not convey Agency judgement of priority for filling data needs. Please do not prioritize data needs.

In stating what information currently exists, be specific, and pay particular attention to routes of exposure and threshold effect levels, when appropriate. Draw conclusions based on the information identified. If there does not appear to be a need for additional information at this time, state this. For example, "Analytical methods are available for measuring carbon tetrachloride in air, water, soil, and solid waste, and most of these methods have good sensitivity and specificity." If there are no data, give reasons why there may be a shortage of data in that area. For example, particular routes of exposure may not be relevant or there may not exist a known exposed population necessary for an exposure registry. If appropriate, state what additional information would be useful and why.

Justify the need for additional research by relating how the information will aid in assessing potential toxicity or human exposure, with particular focus on the exposure conditions of concern at or near hazardous waste sites. Clearly state the need for all additional research. Consider supplementing all data needs with related substance information as appropriate.

GUIDANCE FOR INDIVIDUAL SECTIONS

Chapter 3 Data Needs

General

Present human data (inhalation, oral, and dermal) before animal data (inhalation, oral, and dermal). For each of the three exposure routes (inhalation, oral, and dermal) for which insufficient data have been identified, additional studies should be proposed.

Acute-Duration Exposure

1. Is there sufficient information in humans (or several animal species) to identify target organs following exposure via all three routes? Do the animal data support the human data? Comment, as necessary, on the appropriateness of the animal species. *Remember that the emphasis is on target organs in humans.*

2. State whether the data were sufficient to derive oral and inhalation MRLs. If not, state what information is lackingCeither inadequate identification of target organs or levels of exposure (LOAELs or NOAELs) that cause the effect.

3. In the absence of route-specific toxicity data, state whether pharmacokinetic data are available that may support the identification of target organs across routes of exposure. The end result may be that qualitatively we would expect similar endpoints, but the levels (that cause the effects) may or may not be possible to predict.

4. Lethality data are generally needed only to place other toxicity information into perspective; it is unlikely that additional lethality data will ever be requested.

5. State what additional route-specific exposure information is necessary.

6. Purpose: There are populations surrounding hazardous waste sites who might be exposed to the substance for brief periods; therefore, this information is important.

Intermediate-Duration Exposure

1. Same as Acute-Duration Exposure items 1-5.

2. Purpose: There are populations surrounding hazardous waste sites who might be exposed to the substance for similar durations.

Chronic-Duration Exposure and Cancer

Chronic toxicity data and carcinogenicity data should be discussed in order using two separate paragraphs.

Chronic Toxicity Data

1. Same as Acute-Duration Exposure items 1-5.

2. Purpose: There are populations surrounding hazardous waste sites who might be exposed to the substance for similar durations.

Carcinogenicity Data

1. Discussion should focus on the qualitative evaluation of carcinogenic potential across routes of exposure and the mechanism(s) of action.

2. Regarding mechanism(s) of action, draw needs from peculiarities noted in the data, i.e., bolus versus nonbolus effects, vehicle effects, initiation versus promotion, route-specificity, etc.

3. In the absence of route-specific data, state whether pharmacokinetic data may support the carcinogenic potential of the substance across routes of exposure.

4. Because the Agency has not formally adopted a nonthreshold policy for carcinogens or the use of modeling to derive low-level risks, it is not appropriate to request additional studies for purposes of generating data necessary for modeling.

Genotoxicity

1. Do human data indicate whether the substance may act by a genotoxic mechanism?

2. Do *in vivo* animal data (and/or *in vitro* studies) lend support to the substance's genotoxic potential?

3. In the absence of genotoxicity data, are there "structural alerts" (e.g., electrophilic centers) that suggest the substance is genotoxic?

4. What additional *in vivo* and *in vitro* studies would be important to either confirm or refute the substance's genotoxic potential? If either the *Salmonella* mutagenicity test or an *in vitro* test for chromosome aberrations is positive, consider requesting *in vivo* tests of chromosome aberrations in (known) exposed humans or animals.

5. If genotoxicity testing has only been performed at the maximum tolerated dose (MTD), consider suggesting lower dose values.

Reproductive Toxicity

1. When developing this discussion, remember that the Agency places extreme importance on the acquisition of reproductive toxicity data; in fact, it is desirable to have such data from inhalation and oral routes prior to developing MRLs.

2. State whether there is sufficient information in humans (or several animal species) to indicate whether the substance affects reproductive health following exposure via all three routes. Do the animal data support the human data? *Remember that the emphasis is on human health significance.*

3. In the absence of route-specific data, state whether pharmacokinetic data may support the substance's potential to affect reproduction across routes of exposure. The end result may be that qualitatively we would expect similar health outcomes, but the levels (that cause reproductive effects) may or may not be possible to predict.

4. If intermediate-duration (90-day) studies are needed, consider including discussion of this data need, i.e., reproductive organ pathology should be examined in the 90-day study.

5. Multigeneration studies could be recommended after data are available to indicate that the reproductive system might be a target organ.

Developmental Toxicity

1. Similar to reproductive health outcomes, the Agency places importance on assessment of developmental toxicity; it is desirable to have such data from inhalation and oral routes prior to developing MRLs.

2. State whether there is sufficient information in humans (or in several animal species) to indicate whether the substance affects development following exposure via all three routes. Do the animal data support the human data? *Remember that the emphasis is on human health significance.*

3. In the absence of route-specific data, state whether pharmacokinetic data may support the substance's potential to affect development across routes of exposure. The end

result may be that qualitatively we would expect similar health outcomes, but the levels (that cause the effects) may or may not be possible to predict.

Immunotoxicity

1. Is there reason to believe that the immune system is a target for this substance, either from empirical data or from references from related substances? For example, were there any effects on lymphoid tissue or blood components (peripheral lymphocytes) in the 90-day study? If the answer is a resounding "no," it may be possible to conclude that no additional information is needed at this time.

2. If the answer above is "yes" (please refer to the section where Immunological and Lymphoreticular Effects are discussed), has a battery of immune function tests been performed?

3. Is there any reason to suspect the effects may be route- or species-specific?

Neurotoxicity

1. Is there reason to believe that the nervous system is a target for this substance, either from empirical data or from inferences from related substances? Specifically, is there behavioral, histopathological, neurochemical, or neurophysiological information? If not, it may be possible to conclude that no additional information is needed at this time.

2. Is there any reason to suspect the effects may be route- or species-specific or age-dependent?

3. If there a substance is an adult neurotoxin, developmental neurotoxicity should be studied.

Epidemiological and Human Dosimetry Studies

1. Describe any human studies that are currently available and their limitations.

2. Is there likely to be an identifiable subpopulation in the general populace and/or in the workplace potentially exposed to the substance?

3. Discuss the type of study that might be proposed, and highlight endpoints for which there is information from animal studies or from case studies suggesting that those endpoints may be of concern.

4. Relate how this information will be useful for establishing cause/effect relationships and future monitoring of individuals living near hazardous waste sites.

Biomarkers of Exposure and Effect

Chapter 1 of *Biological Markers in Reproductive Toxicology* (NAS/NRC 1989) provides a good general discussion of this topic. A copy of this reference is being provided to each contractor. This data need should contain the following two subheadings.

Exposure. A biomarker of exposure is an exogenous substance, or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured within a compartment of an organism (e.g., measurement of the parent compound or its metabolite(s), DNA adducts, etc.).

1. Identify known biomarker(s) of exposure for the substance, and state what biological materials should be monitored to determine (a) short-term exposure, (b) intermediate-term exposure, and (c) long-term exposure.

2. State whether the identified biomarkers are specific for the substance (e.g., metabolites).

3. If the parent compound(s) or its metabolite(s) are the only known biomarkers, discuss the usefulness of developing alternative biomarkers to complement this analysis (e.g., sensitivity may be a problem, and you may wish to refer the reader to Chapter 7, Analytical Methods).

4. Keep in mind that the purpose for developing a biomarker is often to facilitate future medical surveillance, which can lead to early detection and possible treatment.

5. Identify the data needs and why they are needed.

Effect. For the purpose of this data need, a biomarker of effect is a measurable biochemical, physiological, or other alteration within an organism that, depending on the magnitude, can be recognized as an established or potential health impairment or disease.

1. Identify known biomarker(s) of effect (i.e., enzyme levels, lymphocytes, aberrations) for the substance, and state what biological materials should be monitored to

determine effects resulting from (a) short-term exposure, (b) intermediate-term exposure, and (c) long-term exposure. State whether the biomarker can be used for dosimetry or is only indicative of effect.

2. Identify the data needs and why they are needed.

Absorption, Distribution, Metabolism, and Excretion (ADME)

This data need should discuss these parameters by route and duration of exposure; the subsequent data need should describe toxicokinetics across species.

1. Is information available to assess relative rates and extent of ADME regarding the three routes of exposure?

2. Are there differences in ADME regarding time or dose, i.e., do saturation phenomena come into play?

Comparative Toxicokinetics

This data need should examine toxicokinetics across species; the preceding data need (ADME) should describe route- and duration-specific pharmacokinetic needs.

1. Are both human and animal data available, and do they indicate similar target organs?

2. Have toxicokinetic studies been performed in both humans and animals? What do these studies show, i.e., are rats a good model?

3. Have toxicokinetic studies been performed in multiple species? If so, are results similar, and would it be reasonable to expect humans to handle the substance similarly (and have similar target organs)?

Methods for Reducing Toxic Effects

This data need should examine the existing clinical and experimental methods of reducing both short- and long-term toxic effects of exposure.

1. Is the mechanism(s) of absorption of the substance known? If so, are there established methods or treatments for reducing absorption following exposure? Note

that these methods are useful only immediately following exposure to the toxic substance. If the mechanism(s) is not known, state this as a data need. Is the mechanism(s) of distribution of the substance in the body known? If little is known regarding distribution of the substance, state this as a data need.

2. Are there established methods or treatments for reducing body burden of the substance or toxic persisting metabolites? Are these methods sufficient to prevent toxicity following long-term exposure?

3. Is the mechanism of toxic action of the substance known? If not, state this as a data need. If the mechanism of toxic action is known, are there established methods that block this mechanism of toxic action?
4. Are there established methods for mitigation of the health effects that result from exposure? For example, are there treatments to repair damage or improve compromised function?

Ongoing Studies

Identify databases and ways to locate additional information. This is important, because there may be studies in progress that will fill a gap or need.

Chapter 6 Data Needs

Physical and Chemical Properties

1. Do we know enough about the chemical and physical properties (i.e., log K_{ow}, log K_{oc}, Henry's law constant, vapor pressure, etc.) of the substance to permit estimation of its environmental fate?

2. Indicate the need for confirmation when toxicokinetic, physical, or chemical information is used to predict the fate of a substance.

Production, Import/Export, Use, and Disposal

In the absence of information on the number of people potentially exposed to the substance near waste sites and other sources, this data need should serve as a surrogate for evaluating human exposure potential. Include an introductory statement based on the information that supports the potential for human exposure to the substance. For example, if the production volume of the

substance is high and its usage is widespread in the home, in the environment, and in industry, then the risk for human exposure may be substantial.

1. **Production**. Do we know whether the substance is currently produced and, if so, in what quantity? Do we know if this amount is larger or smaller than in the past? Do we know what production might be in the future?

2. **Use**. Do we know whether the substance is widely used in the home, environment, or workplace? Do we know if it is a food contaminant?

3. **Release**. Considering typical releases of the substance in the home, environment, and workplace, which environmental media are likely to be contaminated with significant quantities of the substance?

4. **Disposal**. Are current disposal methods efficient, and is there a need to improve them? Is there information on the amounts of the substance disposed of by each method?

5. **Regulatory information**. Do we know if there are rules and regulations governing disposal of the substance?

Environmental Fate

1. Do we know whether the substance partitions in the environment? If so, in what media? Do we know whether the substance's mobility has been characterized in soil?

2. Do we know whether the substance is transported in any environmental medium? If there is no information on the half-life of the substance, this should be considered a data need. To determine the half-life of a substance in water, soil, and sediment, was field testing or microcosms used? Or is the information from controlled lab experiments? How relevant are the data to real-life situations?

3. Do we know whether the substance is degraded or transformed in each environmental medium? Does it persist in some media? Include the fate of degradation products.

Bioavailability

1. State whether the substance is known to be absorbed following inhalation, oral, or dermal contact.

2. State whether there is any information on absorption (bioavailability) of the substance from contaminated air, water, soil, or plant material. If not, can predictions be made?

For example, if a substance is poorly absorbed from the gut and it has a very large K_{oc} value, can anything be predicted about its bioavailability following ingestion of contaminated soil?

Food Chain Bioaccumulation

1. Do we know whether the substance is bioconcentrated in plants, aquatic organisms, or animals (i.e., elevated tissue levels indicating storage in the organism as a result of exposure to contaminated media)?

2. Do we know whether the substance is biomagnified (increased levels in predators resulting from consumption of contaminated prey organisms)?

Exposure Levels in Environmental Media

1. Has the substance been detected in air, water, soil, plant materials, or foodstuffs? *Remember that the focus is on media surrounding hazardous waste sites.* If not, have any environmental monitoring studies been done? If so, are the data current (within 3 years)? Add the following boilerplate.

   Reliable monitoring data for the levels of [substance x] in contaminated media at hazardous waste sites are needed so that the information obtained on levels of [substance x] in the environment can be used in combination with the known body burden of [substance x] to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

2. Have any estimates been made for human intake of the substance from various environmental media?

Exposure Levels in Humans

1. Has the substance been detected in human tissues such as blood, urine, fat, or breast milk? *Remember that the focus is on populations surrounding hazardous waste sites.* If not, have biological monitoring studies been done? If so, are the data current (within 3 years)? Add the following boilerplate.

   This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries

1. Are there known populations that may have unusually high exposures to the substance? *Remember that the focus is on populations surrounding hazardous waste sites.*

2. If so, is there a registry of any population that has been exposed to the substance?

Chapter 7 Data Needs

Methods for Determining Biomarkers of Exposure and Effect

Exposure.

1. For the biomarkers of exposure identified in the Data Needs section of Chapter 3, state whether existing methods are sensitive enough to measure (a) background levels in the population and (b) levels at which biological effects occur.

2. Discuss the precision, accuracy, reliability, and specificity of the methods documented. What are the deficiencies in these areas?

3. Identify the data needed and why they are needed.

Effect.

1. For the biomarkers of effect identified in the Data Needs section of Chapter 3, if appropriate, state whether existing methods are sensitive to measure (a) background levels in the population and (b) levels at which biological effects occur.

2. Discuss the precision, accuracy, reliability, and specificity of the methods documented. What are the deficiencies in these areas?

3. Identify the data needed and why they are needed.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media

1. The purpose of analytical methods is:

    - To identify contaminated areas.

- To determine if contaminant levels constitute a concern for human health.

2. Which media are of most concern for human exposure to the substance?

3. For each medium, are there methods sensitive enough to measure (a) background levels in the environment and (b) levels at which health effects occur?

4. Discuss the precision, accuracy, reliability, and specificity of these methods. What are the deficiencies in these areas?

REFERENCES

1. NAS/NRC. 1989. Biological markers in reproductive toxicology. National Academy of Sciences/National Research Council. Washington, DC: National Academy Press, 15-35.

ATTACHMENT O: GLOSSARY

Absorption -- The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption -- The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) -- is usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model -- is a statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers -- are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Case-Control Study -- A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents

(such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report -- describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Case Series -- describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study -- A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study -- A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs -- substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship -- the quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurrs. The terms, as used here, include malformations and variations, altered growth, and
inutero death.

Environmental Protection Agency (EPA) Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology-- refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity -- a specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life -- a measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Incidence -- The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunological Effects -- are functional changes in the immune response.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

***In Vitro* --** Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo* --** Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO}) -- The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50}) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects -- represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL) -- An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF) -- A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity -- State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality -- Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen -- A substance that causes mutations. A mutation is a change in the DNA sequence of a cell=s DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy -- The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio-- a means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound -- a phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL) -- An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40 hour workweek.

Pesticide -- general classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics -- is the science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Pharmacokinetic Model -- is a set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model -- is a type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model -- is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence -- The number of cases of a disease or condition in a population at one point in time.

Prospective Study--a type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Recommended Exposure Limit (REL) -- A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

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 noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the No-Observed-Adverse-Effect Level (NOAEL- from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study -- A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to casual factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk -- the possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor -- An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio-- The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL) -- The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic -- The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF) -- A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using Lowest-Observed-Adverse-Effect Level (LOAEL) data rather than No-Observed-Adverse-Effect Level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic -- any chemical that is foreign to the biological system.

ATTACHMENT P: ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	Drinking Water Exposure Level

ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	trans,trans-muconic acid

MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM-TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA

OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States

UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
-	negative
+	positive
(+)	weakly positive result
(-)	weakly negative result

ATTACHMENT Q: STANDARDIZED ABBREVIATIONS TO BE USED IN THE LEGENDS

(C)	capsule
(F)	feed
(G)	gavage, not specified
(GO)	gavage, oil
(GW)	gavage, water
(IP)	intraperitoneal
(IM)	intramuscular
(IT)	intratracheal
(IV)	intravascular
(SB)	subcutaneous
(W)	drinking water
6	indicates that a conversion follows
66	indicates an entire conversion, identical to the preceding one
<	decreased
<<	greatly decreased
>	increased
>>	greatly increased
AB	absorption
ad lib	ad libitum
BC	blood chemistry
BI	biochemical changes
BW	body weight
cardio	cardiovascular
CEL	cancer effect level
cm^2	centimeter squared
CS	clinical signs
d	day(s)
develop	developmental
DI	distribution
DX	developmental toxicity
EA	enzyme activity
EC_{50}	effective concentration, 50% of test animals or systems estimated to respond
EX	excretion
F	female
FI	food intake
FM	fecal metabolites
g	gestation
gastro	gastrointestinal
gen	generation
gn pig	guinea pig
Gd	gestation day
GN	gross necropsy
hemato	hematological

HP	histopathology
hr	hour(s)
ID_{50}	dose producing 50% immunodepression
immuno	immunological
kg	kilogram
LC_{50}	lethal concentration producing 50% kill
Ld	lactation day
LD_{50}	dose producing 50% death
LOAEL	lowest-observed-adverse-effect-level
M	male
m^3	cubic meter
mg	milligram
min	minutes
mo	month(s)
musc/skel	musculoskeletal
MX	maternal toxicity
NA	not applicable
NOAEL	no-observed-adverse-effect level
NS	not specified
neuro	neurological
oc	ocular
once	in exposure column, a single dose or exposure
OR	organ function
OW	organ weight
ppd	postparturition day
pg	postgestation
repro	reproductive
resp	respiratory
RM	respiratory metabolites
skel	skeletal
TG	teratogenicity
TM	tissue metabolites
TWA	time-weighted average
UM	urinary metabolites
UR	urinalysis
v/v	volume per volume
WI	water intake
wk	week(s)
wt	weight
w/v	weight per volume
w/w	wet weight
yr	year(s)

Source of conversion factors used in the supplemental document: EPA. 1988. Recommendations for and documentation of biological values for use in risk assessment. Office

of Health and Environmental Assessment. Cincinnati, OH: Environmental Criteria and Assessment Office. EPA-600/6-87-008.

Attachment R: Literature Search Strategy for Child Health Issues

1. Selection of databases to search.

The suggested databases that should be searched are these:

- Medline,
- Toxline,
- Embase, and
- BIOSIS.

Two additional databases should be searched when issues of exposure through food and carcinogenicity are even remotely suspected:

- CAB and
- Cancerlit.

2. Searches should use both chemical name(s) and CAS registry numbers.

3. MESH headings and keywords.

Medline, Toxline, and Cancerlit use MESH headings, at least since about 1985. Medline has used MESH headings since its inception in 1966, Cancerlit since 1980, and Toxline since 1985. However, Toxline use of MESH headings appears to be incomplete for all of its subfiles– even for more recent citations.

If you use direct search engine on Medline or Toxline themselves, such as those available on CD ROM or other government central servers, then use MESH headings specifically. In the case of using a literature search service, such as Dialog, specifying MESH headings is not critical, because the MESH headings, both major and minor, are accessed through the "Descriptor" field along with other keywords.

A. The following MESH headings and descriptors are recommended for both types of searches – "Dialog" or Medline/Toxline.

- zygote
- embryo
- fetus
- newborn
- child
- adolescence
- infant
- age factor (optional)

Additional descriptor field terms can be used, but they appear to add little to the searches and they are not MESH headings by themselves. This will add unnecessary citations to the searches.

B. An additional search of the following terms in the title and abstract fields should be added to the descriptors presented above in section A.

- wean? [the ? means for the search engine to accept any suffix letters following it]
- offspring
- postnatal

The following terms often are used in titles, abstracts or descriptor fields for citations of interest, but they do not appear to add citations that would not be picked up by the terms listed above. They most likely add unnecessarily to the searches.

Fetal, juvenile, prenatal, neonatal, postpartum, terato?, utero?, boy, girl, teen, infancy, gestation.

4. Limiting the search by one or more following fields may be valuable, under some circumstances:

- Year of publication, e.g., PY=1970-1990.
- Language, e.g., LA=English (not usually recommended).
- Type of publication, e.g., Review articles only.

5. The DART database of the National Library of Medicine is an active database of publications that include developmental and reproductive toxicology topics. It is also a subfile in TOXLINE, but new DART records are only added 2 to 3 times a year to TOXLINE, so there is a slight lag for up to 2000 new records when compared with records from NLM/DART directly. If these end points are critical and new research might be ongoing, and then consider a direct search of DART. Otherwise, it is likely to add very little to the body of literature for a particular chemical.