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Final External Review

Considerations for Developing Alternative Health Risk Assessment Approaches for Addressing Multiple Chemicals, Exposures and Effects (External Review Draft)

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LIST OF ABBREVIATIONS

The main acronyms and abbreviations used in this guidance document are identified below. Where use is essentially limited to tables or equations, the term is specified with those tables and equations. Where use is primarily in an appendix, the term is specified in that appendix.

ARARs	applicable or relevant and appropriate requirements
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BAF	bioaccumulation factor
BCF	bioconcentration factor
BMD	EPA benchmark dose
BMDL	lower confidence limit on BMD
BP	boiling point
BTEX	benzene, toluene, ethylbenzene, and xylene
°C	degrees Celsius or centigrade
CDC	Centers for Disease Control and Prevention
CEP	Cumulative Exposure Project
CERCLA	Comprehensive Environmental Response, Compensation, & Liability Act
CSM	conceptual site model
DBP	disinfection byproduct
DCE	dichloroethylene
DDT	dichlorodiphenyltrichloroethane
DNA	deoxyribonucleic acid
DNAPL	dense nonaqueous phase liquid
DOE	U.S. Department of Energy
EPA	U.S. Environmental Protection Agency
ETS	environmental tobacco smoke
foc	fraction of organic carbon
GIS	geographic information system
HAP	hazardous air pollutant
Hg	mercury
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System (EPA database)
Kd	soil-water partition coefficient
K_H	Henry's constant

LIST OF ABBREVIATIONS cont.

Kow	octanol-water partition coefficient
Ksp	solubility product
L	liter
LNAPL	light nonaqueous phase liquid
LOAEL	lowest observed adverse effect level
log Koc	logarithm of the soil organic carbon-water partition coefficient (centimeter^3 water per gram carbon)
log Kow	logarithm of the octanol-water partition coefficient (centimeter^3 water per centimeter^3 octanol)
m^3	cubic meter
mg	milligram
mg/kg	milligram per kilogram
mg/kg-day	milligram per kilogram body weight per day
mm	millimeters
mol	moles
MP	melting point
MSA	metropolitan statistical area
NAS	National Academy of Sciences
NATA	National Air Toxics Assessment
NCEA	National Center for Environmental Assessment, EPA
NHEXAS	National Human Exposure Assessment Survey
NOAEL	no observed adverse effect level
NPL	National Priorities List (EPA)
NRC	National Research Council (NAS)
OP	organophosphorous (pesticide)
ORD	Office of Research and Development (EPA)
PAHs	polycyclic aromatic hydrocarbons
PBPK	physiologically based pharmacokinetic (model)
PCBs	polychlorinated biphenyls
PD	pharmacodynamics
PK	pharmacokinetics
PM2.5	particulate matter with a diameter of 2.5 μm or less
PM10	particulate matter with a diameter of 10 μm or less
POM	particulate organic matter
ppb	parts per billion
ppm	parts per million
QA/QC	quality assurance/quality control

LIST OF ABBREVIATIONS cont.

RAGS	Risk Assessment Guidance for Superfund (EPA)
RAPIDS	Regional Air Polluntant Inventory Development System
RfC	reference concentration
RfD	reference dose
Sw	solubility in water
TCDD	tetrachlorodibenzo(p)dioxin
TCE	trichloroethylene
TCEQ	Texas Commission on Environmental Quality
TD	toxicodynamics
TK	toxicokinetics
TPA	tris(2-ethylhexyl) phosphate
TRI	Toxics Release Inventory (EPA)
UCL95	upper 95% confidence limits on the arithmetic averages
UF	uncertainty factor
μg	microgram
μm	micrometer
USGS	U.S. Geological Survey
VP	vapor pressure

PREFACE

This report was developed as a joint effort between the U.S. Environmental Protection Agency's (EPA) Office of Research and Development (ORD), National Center for Environmental Assessment - Cincinnati Office (NCEA-Cin) in collaboration with the Department of Energy's Argonne National Laboratory. It offers information that can be used to implement basic cumulative risk concepts within the framework set forth by EPA. The aim is to illustrate approaches and resources that can be used to more explicitly assess cumulative health risks from multiple chemicals for specific sites and situations. This scope can involve evaluating many different sources and contaminants, several media (soil, water, air, and structures) and associated exposure pathways, various representative individuals or population subgroups who could be exposed over time, and multiple health effects. The overall goal of using cumulative risk approaches is to produce more accurate and effective assessments of these sites and situations, leading to more informed and ultimately better decisions for managing potential cumulative health risks. An external review was conducted by …….. under EPA Contract No …….

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EXECUTIVE SUMMARY

U.S. EPA, in its 2003 *Framework for Cumulative Risk Assessment,* defines cumulative risk assessment as the evaluation of risks from exposures to multiple chemicals and other stressors, possibly including multiple exposure routes and times and multiple health endpoints. In addition, cumulative risk assessment has a population focus rather than a source-to-receptor focus. U.S. EPA has published several general and Program Office-specific guidance documents relating to chemical mixture risk assessment. This report is the result of an exploratory effort to provide explicit approaches for addressing some of the complicating "multiples" in cumulative risk assessment. These approaches include new methods and the extension of existing methods to address health risk from multiple chemicals and multiple exposure pathways and times. Quantitative methods are also discussed for characterizing cumulative health risks while taking into account multiple health endpoints and interactions among multiple chemicals. In U.S. EPA's 2000 *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures*, interactions are addressed only in terms of altered or joint toxicity. The approaches in this report extend those ideas to include kinetic modeling to integrate exposures occurring through multiple routes, interactions affecting fate and transport and interactions affecting multi-route joint toxicity. Exposure and toxicity characterizations of mixtures are strongly dependent on mixture composition (chemicals and concentrations) and timing of exposure and health effects. Consequently, recurrent in this report is the emphasis on the iteration and collaboration between exposure assessment and dose-response assessment to ensure compatible and relevant information.

The areas of the 2003 *Framework* addressed herein include primarily the information gathering phase of Problem Formulation and the subsequent phases of Analysis and Risk Characterization. This report discusses technical issues and possible simplifications and shows the feasibility of such a multi-factor assessment using existing information. Specific suggestions are presented to simplify the complexity of a cumulative risk assessment by forming groups of exposures, chemicals or toxic effects with the highest likelihood of significant joint contribution to the cumulative health risk. Although sensitive population groups are often mentioned, there is no detailed guidance on how to identify such groups nor how to quantify the population factors for inclusion in the risk assessment.

This report is not guidance but rather a presentation of concepts that could assist the development of guidance. It presents risk assessment approaches and information on a subset of issues that are identified in the 2003 *Framework for Cumulative Risk Assessment*. The sequence of procedural steps suggested in this report is designed to emphasize the links between the exposed population and the multiple factors being addressed. The audience for this report is anyone involved in chemical risk assessment who needs to address the joint impact of multiple chemicals, exposures and effects.

1. INTRODUCTION TO CUMULATIVE RISK AT THE U.S. EPA

Public interest in the environment continues to grow as more information is shared about multiple chemicals in air, water, and soil from different sources, with health risks being a major concern. The U.S. Environmental Protection Agency (U.S. EPA, or the Agency) has responded to increasing requests for a way to understand and evaluate the combined impacts of these conditions by preparing a set of reports on various aspects of cumulative risk assessment. Those documents have provided information to help explain, scope, and organize cumulative risk assessments. A recent report defined the general framework for these assessments (U.S. EPA, 2003a), and earlier reports laid the broad foundation for the initial stages involving planning and scoping (U.S. EPA, 1997a, 2002a). Additional documents have been prepared to address cumulative risk issues within specific programs, and further efforts are under way.

This document is an initial step toward identifying specific approaches for implementing cumulative health risk assessments. This report is not a regulatory document and it is not guidance, but rather a presentation of concepts that could assist the overall EPA development of Program specific approaches and cumulative risk guidance. Building on the concepts that have been identified in earlier reports and offering examples to illustrate how those concepts can be applied, this report focuses on approaches for assessing health risks associated with multiple sources, chemicals, exposures and effects, with examples pertaining to contaminated sites, drinking water, and ambient air. Most of the approaches described in this report can also be applied to assess similar risk issues beyond the example applications. It must be emphasized that

"cumulative risk assessment is not going to be appropriate to every task; it is most useful when addressing the risks from multiple stressors acting together" (U.S. EPA, 2003a).

The purpose and scope of this report, including its relationship to other U.S. EPA cumulative risk documents, is explained in Section 1.1 with the report organization summarized in Section 1.1.4. A brief overview of key examples of existing U.S. EPA approaches from which this integrated approach has evolved is provided in Section 1.2, and the overview of the integrated approach for multiple chemicals, pathways, timeframes, and effects is given in Section 1.3.

1.1. PURPOSE AND SCOPE OF THIS REPORT

The purpose of this report is to describe information and risk assessment approaches that can be used to implement the basic cumulative risk concepts set forth in the U.S. EPA's *Framework for Cumulative Risk Assessment* (U.S. EPA, 2003a), but with a reduced scope and a limited number of example applications. The intent is to illustrate that approaches and resources are available to more explicitly assess the multifactor aspects of cumulative health risks for specific scenarios and sites. Because of the variety of these scenarios, such an assessment can involve evaluating many different sources and contaminants, several media (soil, water, air, and structures) and associated exposure pathways, various representative individuals or population groups who could be exposed over different time frames, and multiple health effects. The overall goal of using cumulative risk approaches is to produce more accurate and effective assessments of these sites and situations, leading to more informed and

ultimately better decisions for managing potential cumulative health risks (see Text Box 1-1).

By addressing many different pieces of the risk picture together, from sources to effects, this report is designed to support an assessment of "integrated multiples" for human health, as highlighted in Figure 1-1. With stressors limited to chemicals and effects limited to human health, this scope is much narrower than that of a comprehensive assessment that would cover all of the aspects of cumulative risk described in the framework document (U.S. EPA, 2003a). Such a comprehensive cumulative risk analysis would also address other stressors (including physical and biological agents, as indicated) and their additional sources, and it would integrate effects on other kinds of receptors (e.g., ecological) and resources (e.g., sociocultural) to evaluate several types of risks or impacts, as illustrated in the background of Figure 1-1.

This Report: Basic Q&A *(Text Box 1-1)*

What kind of risk?	Human health, joint & multiple effects
From what/where?	Multiple chemicals, sources, routes
What time frame?	All, including mixed time frames
Why?	To address public concerns over elevated toxicity from multiple sources, exposures, or effects

A key reason for the targeted scope of this report is to focus first on a stated need. Many communities near contaminated sites, large agricultural areas or in industrial cities have voiced concerns about the combined effects of multiple chemicals on public health. Awareness of chemical-chemical interactions is also high. For example, many news articles of risks from pesticides have focused on exposure to multiple pesticides, including those designed to have synergistic component chemicals. The Agency for Toxic Substances and Disease Registry (ATSDR) conducts public health consultations that routinely address exposures to chemical mixtures and

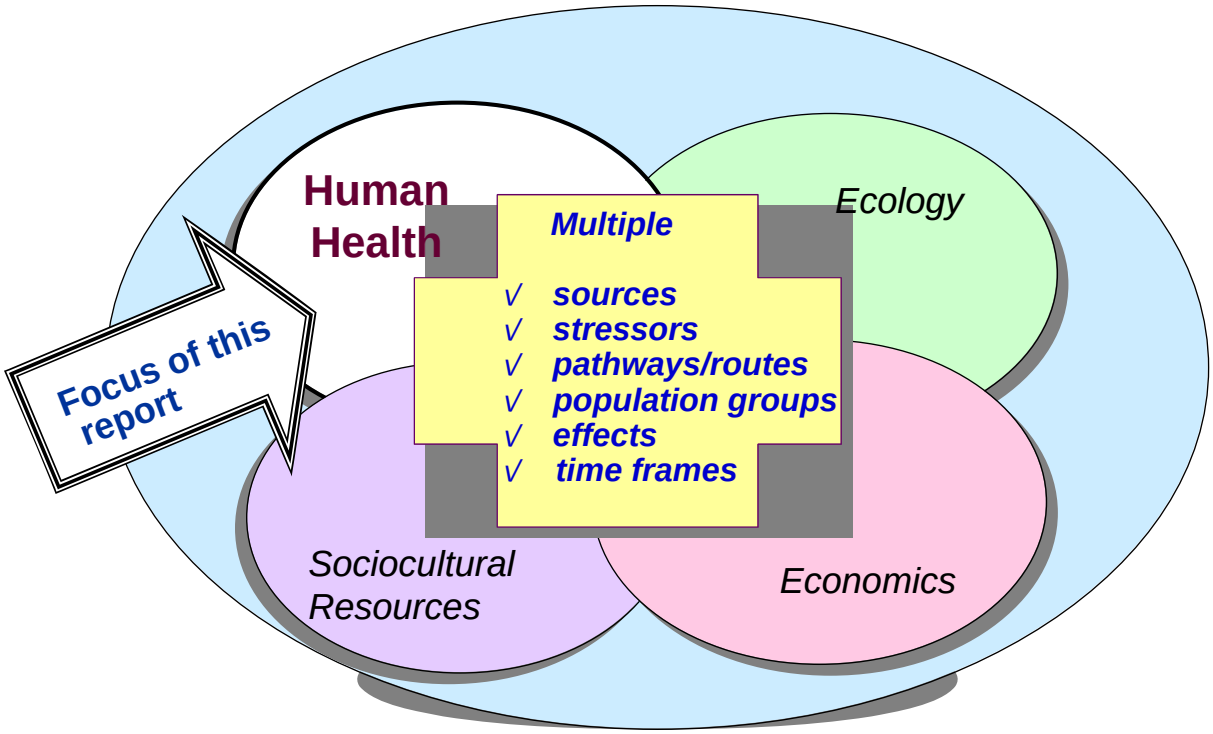


FIGURE 1-1

Assessing Integrated Multiples: Focus on Human Health

maintains a Web site containing chemical profiles on toxicity and toxicologic interactions (http://www.atsdr.cdc.gov). A second reason for the scope being limited to chemicals is that U.S. EPA has regulatory guidance and newly proposed methods to assess risk from exposures to multiple chemicals and pathways, so that addressing these multiples is often possible with only slight modification and integration of existing tools.

To summarize, the purpose of this report is to provide a structured collection of approaches for addressing the chemical interactions and joint toxicity issues in cumulative health risk assessment by describing key concepts and illustrating steps that can be taken to more explicitly evaluate cumulative risks. This report builds on recent U.S. EPA documents (highlighted in the following sections) to extend their concepts into a first phase of implementation that addresses the joint and interactive impacts of multiple chemicals, exposures and effects. Chemical and toxicologic interactions are a primary focus because these are areas where methodological advances allow the traditional process (evaluating chemicals individually) to be enhanced. Approaches for grouping are presented in order to simplify complexities and combine components for joint analysis, so attention can be focused on the factor combinations that could contribute most to adverse cumulative health risks.

1.1.1. Cumulative Risk Framework. The *Framework for Cumulative Risk Assessment* (U.S. EPA, 2003a) identifies three phases of a cumulative risk assessment. (1) problem formulation, (2) analysis, and (3) risk characterization (see Figure 1-2). Planning and scoping, an iterative dialogue between the technical scientists, risk managers and stakeholders, takes place mostly during problem formulation, but may be revisited as needed during the risk analysis and risk characterization phases.

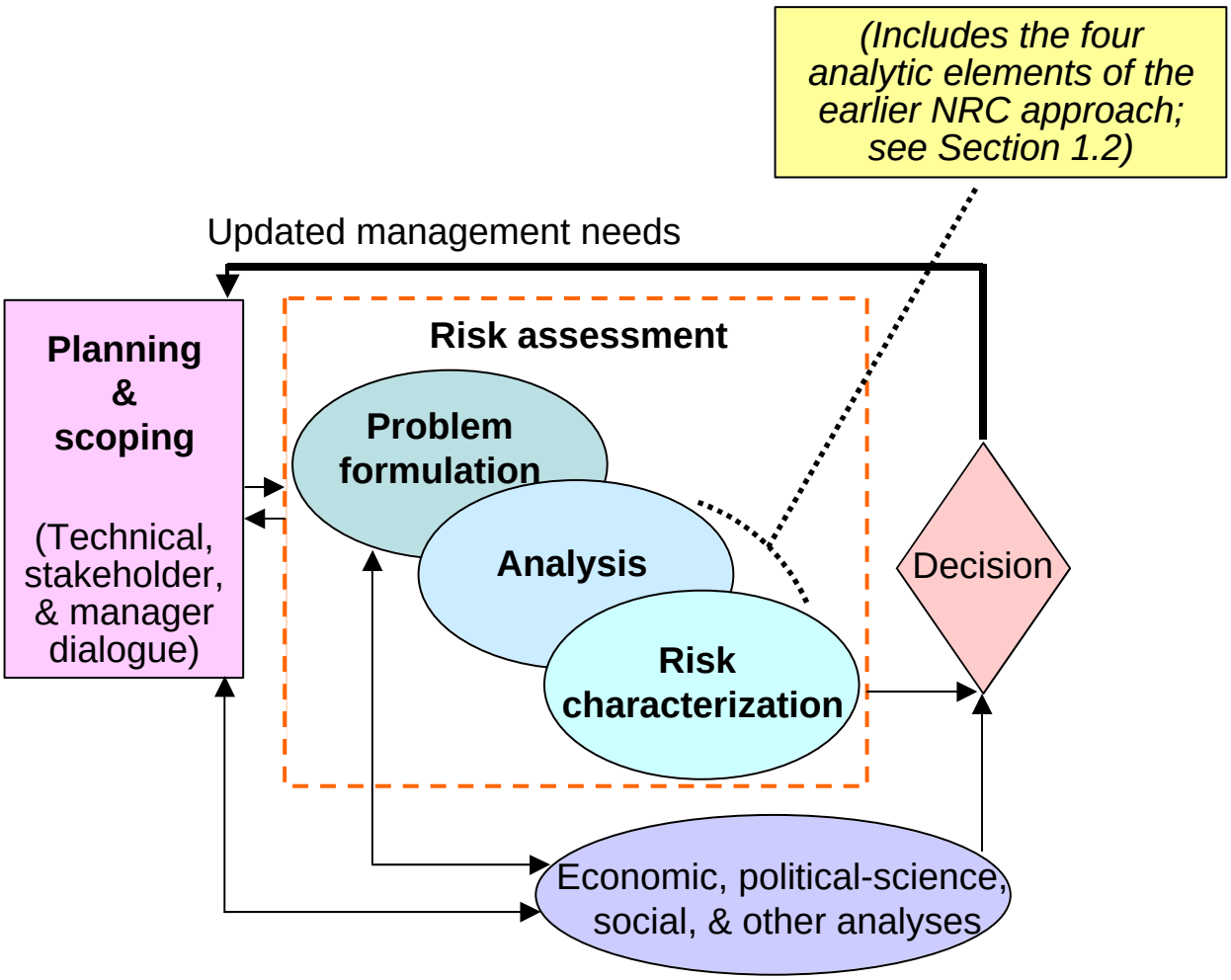


FIGURE 1-2

Integrated Process for Cumulative Risk Assessment
(Source: adapted from U.S. EPA, 2002f)

During the problem formulation phase, the goals, breadth, depth, and focus of the assessment are established by a team of risk assessors, risk managers and other stakeholders, producing a conceptual model and an analysis plan. The conceptual model establishes the stressors to be evaluated, the health or environmental effects to be evaluated, and the relationships among various stressor exposures and potential effects. The analysis plan lays out the data needed, the approach to be taken, and the types of results expected during the analysis phase.

The analysis phase in the framework includes the determination of the analytic and calculation methods to use for exposure assessment, dose-response assessment, and risk estimation. In contrast to the NRC risk assessment paradigm for single chemicals, the exposure and dose-response processes for cumulative risk are expected to occur simultaneously and iteratively to ensure information compatibility. Because of this interaction, this phase also includes the initial estimates of joint health risk from the multiple stressors (chemicals, in this report) to which the study population and sensitive population subgroups are exposed (U.S. EPA, 2003a, p. xviii).

The final phase, the risk characterization, involves further analysis so that the risk estimates are placed into perspective in terms of significance and uncertainties. It is also where the risk assessment process is evaluated to determine whether the objectives and goals of the first phase (planning, scoping, and problem formulation) have been met. The present report does not address planning and scooping, but begins with the activity in the problem formulation part of the first phase, i.e., the initial development of the list of chemicals and effects of concern as well as the preliminary

characterization of the population assessed. The report then continues on to describe approaches for the analysis and risk characterization phases.

1.1.2. Relationship to Other Programs and Documents. This report is closely linked to, and relies upon, several key guidance documents across U.S. EPA, as illustrated by the examples in Figure 1-3. The Agency has been addressing many aspects of cumulative risk assessment for some time. The Office of Research and Development (ORD) has prepared and coordinated a number of major reports that cover the topics shown in the following paragraph, and other U.S. EPA Program Offices have developed issue papers and guidance reports on some of the key factors in cumulative risk assessment. The general scope and timeline of these documents are highlighted in Figure 1-4. (There are several other Agency guidance documents and reports that address issues related to risk assessment, such as Data Quality Objectives, but do not explicitly address the multiples issues of cumulative risk; they are discussed in Appendix A.) Dates shown on that figure are for selected major reports within the program areas; additional documents are described in the following chapters (e.g., see U.S. EPA, 2001a, 2002a,b, 2003b). Other reports are underway; for example, a follow-up report on the National Air Toxics Assessment (NATA) air toxics study of 1999 data is expected soon, and guidance for addressing PCBs by combining mixture data with information on the component chemicals is under review. Documents developed by other organizations (such as the Agency for Toxic Substances and Disease Registry, ATSDR) to support cumulative health risk analyses are described in other sections of this report.

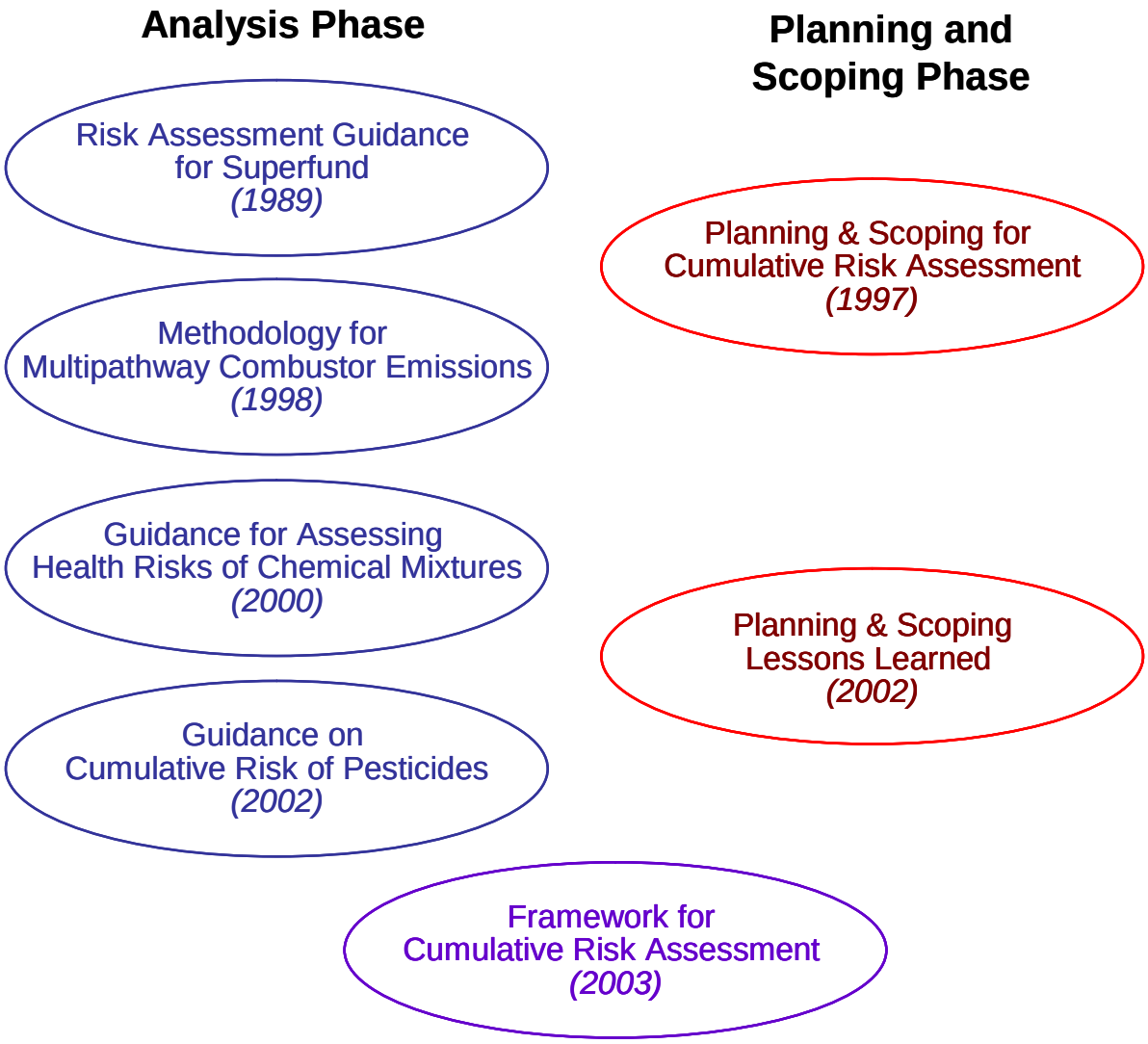


FIGURE 1-3

Key U.S. EPA Resources for this Report: Precedent U.S. EPA Guidance and Reports Containing Specific Approaches for Assessing Major Parts of Cumulative Health Risks

The documents shown in Figure 1-4 focus on distinct parts of the cumulative risk picture rather than covering all aspects described in the U.S. EPA cumulative risk framework. This is because those reports were prepared to address specific issues, as defined by (1) a regulatory requirement, e.g., for air toxics, pesticides, and drinking water, (2) a public demand, e.g., for community-based studies, or (3) a new assessment approach or policy, e.g., for mixtures, and planning and scoping. Other reports will continue to be developed to address the various steps and issues in the U.S. EPA framework.

To illustrate how certain cumulative risk topics are not covered when the scope is limited to a targeted issue, consider three reports highlighted in Figure 1-4, each of which focuses on health risks (i.e., only one risk type is being addressed). The national air toxics study of more than 30 priority urban air toxics does not address toxic interactions (the dose-additivity and risk-additivity defaults are applied), the pesticide assessment only focuses on a limited set of organic compounds (which act by the same toxic mode of action to exert the same general effect), and the mixtures guidance does not address aggregate exposures (only multiple chemicals by the same route). Several existing U.S. EPA risk guidance documents, however, contribute substantially to the approaches for addressing major issues with cumulative risk. Three of the more influential guidance documents are discussed in more detail in Section 1.2.

1.1.3. Scope and Terminology. The scope of this report has been limited to one type of risk (health) for one type of stressor (chemicals) so it can remain manageable while still addressing a specific need. Thus, only a subset of the full range of cumulative risk issues is covered here. For example, while multiple chemicals and exposures and both

Chemical mixtures
What: health risks for whole mixtures, for combinations of similar, independent, & interacting chemicals
Why: update 1986 guidelines for multiple chemicals to enhance methods
Who: National Center for Environmental Assessment
When: 2000 (guidance)

Pesticides
What: health risks for common mode of action, multiple exposure routes
Why: address Food Quality Protection Act "no harm" requirements
Who: Office of Pesticide Programs
When: 1999-2002 (guidance and organophosphates assessment)

Community-based pilot studies
What: range of multiple urban chemicals/sources, exposures, health effects
Why: address public concerns about combined risks in urban communities
Who: Regional Offices, with local organizations and citizen groups
When: late1990s – 2004 (individual studies)

National air toxics assessment
What: inhalation health risks of outdoor air toxics from multiple sources
Why: define baseline & driving chemicals/sources, prioritize data collection
Who: Office of Air Quality Planning and Standards
When: 2001 (national-scale report for 1996 data, updates coming)

Disinfection byproducts in water
What: health risks of multi-route exposures to water treatment residuals
Why: address Safe Drinking Water Act "complex mixtures" requirements
Who: National Center for Environmental Assessment
When: 2003 (initial risk report, other reports coming)

Planning and scoping for cumulative risk assessment
What: description of concepts for up-front thinking to lay out process
Why: guide the first step, emphasizing broad scope & integrated dialogue
Who: Office of Science Policy
When: 1997 (guidance)

Planning and scoping lessons learned
What: summary of experience from studies since the 1997 guidance
Why: encourage formal planning & scoping of environmental assessments
Who: Office of Science Policy
When: 2002 (report with case studies)

Research needs for cumulative risk assessment
What: user-based evaluation of current programs, approaches, and needs
Why: focus and prioritize Agency research, leverage interagency efforts
Who: Office of Science Policy, with Regional Offices
When: 2002 (workshop summary)

Framework for cumulative risk assessment
What: description of umbrella issues, concepts, and general approaches
Why: guide overall integrated organization for many types of assessments
Who: Risk Assessment Forum
When: 2003 (framework report)

Case studies for cumulative risk assessment
What: summary of examples, including community-based pilot studies
Why: provide insights to help others conduct cumulative risk assessments
Who: Risk Assessment Forum
When: 2005 (effort underway, no report yet)

Novel health risk assessment approaches for addressing multiple chemicals, exposures and effects
What: combined health risks for multiple chemicals, pathways, effects
Why: provide simplifying methods and show feasibility
Who: National Center for Environmental Assessment
When: 2005 (this report)

FIGURE 1-4

Highlights of Recent Cumulative Risk-related Program Guidance and Research Reports

cancer and noncancer health endpoints are addressed, approaches for interactions with non-chemical stressors, such as noise, or for other kinds of risk are not included. The important issues related to stakeholder involvement are also not included. Nevertheless, within its targeted scope, this report does address each of the main analysis and characterization steps involved in implementing a cumulative risk assessment, and most of the approaches should be applicable to broader types of stressors, complex exposures, interactions, and multiple effects. Specifically, the initial steps in the framework of planning and scoping and of problem formulation are not discussed in any detail here, with the focus instead on information gathering, analysis and risk characterization. The technical topics in cumulative risk assessment included in this report are

- population characterization
- exposure to multiple chemicals
- exposures by multiple pathways considering different time frames
- potential toxicologic interactions considering time frames of kinetics and effects
- multiple health endpoints and
- characterization of cumulative risks and the attendant uncertainty.

Terminology often used for cumulative risk assessment overlaps primarily with terms of mixture risk and population sensitivity. Some of the more common terms are defined in Text Box 1-2. Fuller definitions for these and other terms in this report are provided in the glossary (Chapter 7).

For U.S. EPA, *cumulative risk assessment* involves combined risks from multiple exposures to multiple *stressors* (chemicals are the focus here) from all contributing

sources. This assessment addresses a given *receptor population*, whether this be an actual community or an imaginary group (such as projected possible residents of a cleanup site). This integrated approach then extends beyond assessments that produce separate estimates for each contributing *source* (such as releases from a waste pit, emissions from an incinerator, or effluent from a wastewater treatment facility) by estimating risk from the joint exposure via all identified sources.

Key Terms for Cumulative Health Risks *(Text Box 1-2)*

Aggregate exposure	Combined exposure to one chemical; can be from multiple sources, pathways
Cumulative risk	Combined risk from exposures to multiple chemicals; exposures may be aggregate
Effect	Health endpoint estimated from toxicity studies (first-observed is critical effect; secondary effect seen at higher doses)
Exposure pathway	A complete pathway has (1) source & mechanism of release, (2) contaminant fate & transport (through environmental media), (3) point of receptor contact with the source or affected medium, and (4) exposure route
Exposure route	How a contaminant gets inside a person (e.g., via inhalation, ingestion, or dermal absorption)
Environmental interaction	One chemical acting on another to influence fate or transport
Joint toxicity	Toxic action exerted by two or more chemicals acting together
Toxicological Interaction	Joint toxicity that is greater or less than expected under additivity (note: forms of additivity include summing of doses, risks or biological measurements across chemical components of a mixture)
Receptor population	Group actually or potentially exposed
Source	Origin of contaminant (e.g., a landfill)

A cumulative assessment can involve multiple *exposure pathways* and *exposure routes* that reflect different ways contaminants can be taken into the body from different media (e.g., breathing air and drinking water). These assessments also consider multiple *effects* within two main categories: cancer and noncarcinogenic systemic effects. For the latter, a cumulative risk assessment should consider critical and secondary (and higher) effects. The critical effect is the first effect observed as the chemical's dose is increased above a no-effect range in the relevant toxicity study, and it serves as the basis for the Reference Dose (RfD, see definition in Chapter 7) or other

noncancer toxicity value; secondary and further effects are those seen at higher doses and are rarely incorporated into single chemical risk assessments.

Multiple stressors are central to cumulative risk analyses. If exposures are evaluated for only one chemical, even if it is present from many sources and in different media, and even if it is taken in by multiple exposure routes, the U.S. EPA defines this as an *aggregate exposure assessment*. Because an aggregate assessment only addresses a single chemical, it is not formally considered a cumulative assessment. However, if a set of aggregate exposures is combined, addressing two or more chemicals and their joint effects, then that would constitute a cumulative assessment.

Interactions that consider location and timing are a main emphasis in this report. In the environment, interactions can alter the fate and transport of combined chemicals, e.g., by facilitating mobility in soil or sorption onto air particulates. Once taken into the body, a key emphasis of this evaluation is *joint toxicity*, which is simply the collective toxicity of two or more chemicals. This can be additive (the default assumption), less than additive (antagonism), or more than additive (synergism). The Agency has defined the specific term, toxicological interactions, to represent interactions that are other than additive (U.S. EPA, 2000a). The Agency has developed an interaction formula based on departures from dose addition (see Chapter 4). Toxicological interactions are then commonly defined by U.S. EPA as those that result in effects that are either lower or higher than expected from the individual chemicals acting under an assumption of dose additivity, such as the synergistic effect of cadmium and lead on the neurological system or the antagonistic effect of cadmium and lead on the kidney (see Chapters 4

and 5). Such interactions are a common concern at contaminated sites, and they represent an important focus of this initial report.

1.1.4. Report Organization. Cumulative health risk assessment covers a breadth of topics, as explained in the Agency's recent framework document. That is, the process is not limited to combination toxicology, nor does it just involve evaluating how multiple chemicals and multiple exposure pathways can combine to produce adverse health effects in people exposed over time. Rather, the cumulative risk assessment process extends from identifying how the assessment was initiated, to determining how the analysis will be conducted and how results will be presented. This report is organized to cover this range of topics for cumulative risk assessments, as follows.

Chapter 1, Section 1.2 identifies examples of existing U.S. EPA guidance that addresses at least part of the multiples issues with cumulative risk assessment. Section 1.3 presents a summary of the steps in addressing the multiples issues, emphasizing the factors that could trigger the cumulative assessment and the interconnections between these steps.

Chapter 2 discusses the initial characterization of the population and chemicals of concern as influenced by the trigger factor that initiated the cumulative health risk assessment, ending with the initial appraisal of links between environmental exposures and target populations.

Chapter 3 describes exposure assessment concepts and offers resources and approaches that can be used to characterize the setting, group the chemicals and pathways based on joint and interactive processes, and quantify exposures for a cumulative assessment. The influence of toxicity information on the exposure assessment is included.

Chapter 4 explains and illustrates key toxicity concepts, including common target organs and systems, internal overlaps of doses and effects, interaction toxicity, and receptor characteristics that can affect toxicity. The influence of exposure information on the toxicity assessment is included.

Chapter 5 provides information for the risk characterization step, including ways to address uncertainty for cumulative risk assessments and the need for comparison with the goals from the planning and scoping phase.

Chapter 6 identifies reference information for the documents and articles cited in this report.

Chapter 7 defines basic terms used in cumulative health risk assessments.

Supporting details are provided in the appendices.

Appendix A presents a toolbox of selected resources that can be useful in conducting cumulative risk assessments.

Appendix B illustrates how primary toxicity information can be organized to support grouping for cumulative health risk assessments.

1.2. EXAMPLES OF EXISTING U.S. EPA GUIDANCE

The National Research Council issued *Risk Assessment in the Federal Government: Managing the Process* (NRC, 1983), commonly called the red book, over 20 years ago. This document identified four basic steps for risk assessment, which provided the original foundation for risk-based programs across many federal agencies: hazard identification, dose-response assessment, exposure assessment, and risk characterization. These general steps are reflected in most U.S. EPA guidance for assessing risks, such as that under the Superfund program (U.S. EPA, 1989a), which has served for many years as the common basis for contaminated site cleanups and federal and state waste management programs. Other programmatic risk assessment guidance documents, such as those addressing national air standards, drinking water standards, and regulation of pesticides, also are structured roughly along these four steps. Risk assessment other than standard setting is specific to the site or situation of concern and has an additional first step of preliminary analysis of environmental chemical levels. The traditional four steps of the process as applied to assess risks for specific contamination events or sites are summarized in Text Box 1-3.

In risk-based standard setting, contaminants have historically been evaluated one at a time. Consider, however, the example of the assessment of contaminated sites, where more complex exposures are included; chemical exposures are summed across environmental media and exposure pathways to estimate total exposures, cancer risks, and the combined potential for noncancer effects (U.S. EPA, 1989a). Although the basic site assessment guidance calls for considering multiple chemicals, exposure routes, and effects (thus cumulative risks), few specific suggestions were provided that would enable a practitioner to extend beyond the basic additive approach in the original U.S. EPA mixture guidelines (U.S. EPA, 1986), primarily because of limitations in extant understanding of environmental and toxicological interactions.

Summary of Traditional Risk Assessment Steps
(Text Box 1-3)

Hazard identification/ data evaluation	Identify contaminant hazards and determine their levels in various media (soil, water, air)
Exposure assessment	Evaluate who could be exposed, how much
Dose-response assessment	Quantify dose-response relations and define toxicity values from scientific studies
Risk characterization	Describe cancer risks, noncancer effects and related uncertainties

As more has been learned about the environmental behavior and toxicology of chemicals through ongoing research, the risk assessment process has kept pace. Ten years ago the National Research Council recommended moving away from the single-chemical assessment focus (NRC, 1994), and the emphasis has continued to shift toward a receptor- (population-) based focus. As noted in the recent U.S. EPA mixture guidance (U.S. EPA, 2000a), the four originally distinct steps are now closely linked; in particular the exposure and toxicity evaluations should be jointly performed so that the exposure assessment can be refined based on toxicity information and vice versa. During the past several years the Agency has published several cumulative risk

documents (as illustrated in Figure 1-4) that capture this shift and extend assessment concepts well beyond the original basic approach.

The U.S. EPA planning and scoping documents identify iterative problem formulation as a key element of the cumulative risk assessment process (U.S. EPA, 1997a, 2002a). This broadens the process beyond the four original data-driven (analytic) steps by bringing in the key scoping (or deliberative) component. The broad U.S. EPA *Framework for Cumulative Risk* document defines a flexible structure that includes planning, scoping, and problem formulation, as well as specific assessment and characterization issues (U.S. EPA, 2003a). That document describes main concepts and the underlying technical factors across a range of risk types and applications. Together, this set of Agency reports provides a general view of how risk analyses can better reflect real-world conditions. These include complex exposure and effect processes as well as "human interactions" that involve stakeholders and regulators discussing a given risk issue to better understand and address cumulative risks.

These recent Agency documents respond to the public's desire to bring together individual pieces of the environmental risk picture (many of which are regulated under separate federal programs) so risks that consider all sources, stressors, exposures, affected population groups, and effects can be better understood and ultimately better managed. Thus, while the four-step NRC paradigm from two decades ago provided an essential foundation, the approach for assessing health risks from exposures to chemicals in the environment has evolved considerably since then.

One major difference from the historical approach is that today's analyses, in terms of the scope of this report, are more closely integrated with careful attention paid to potential interactions among them. Emerging science is offering new ways to evaluate how one chemical could affect the behavior of another in the environment, how one could affect how another is absorbed, distributed, metabolized, or eliminated from the body, and whether their combined toxicity could differ from that estimated from the single chemical toxicities. This report aims to illustrate how this new information can be applied to better address cumulative health risks. The following sections provide some detail on three existing U.S. EPA guidance documents that form a foundation for addressing the multiplicity issues with the exposure and toxicity assessment steps of cumulative risk, along with brief discussion of their weaknesses that this current document addresses.

1.2.1. Mixtures Risk Assessment. Until recently, the most common application of mixture risk assessment was to Superfund waste sites. The applicable legislation passed in 1980, the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA), specifically calls for the evaluation of risks from mixtures. In the original U.S. EPA mixtures guidelines (U.S. EPA, 1986), the recommended approach was dose or response additivity based on evaluations of individual chemicals. While interactions were discussed and addressing them was recommended (if data were available), no specific approaches were described because toxicologic understanding and quantitative data on interactions were limited. To help address this issue, the Agency recently released guidance for assessing the health risks of mixtures (U.S. EPA, 2000a), which updates the earlier guidelines to provide further

methodological detail that reflects evolving toxicological knowledge. By describing a process for quantitatively evaluating toxic interactions of multiple chemicals, that guidance offers a clear step forward from past practice. Specific approaches address complex mixture risk values, environmental transformations of complex mixtures, toxicologic similarity based on varying evidence (from similar mechanisms to similar target organs), and toxicologic interactions. The main weakness in the 2000 guidance is the lack of approaches for multichemical and multipathway exposure assessment, as well as approaches for multiple effects from mixtures.

1.2.2. Superfund Site Assessment. The standard guidance for assessing site health risks (U.S. EPA, 1989a and subsequent companion documents) calls for consideration of multiple chemicals, sources, exposure routes, receptors, and effects. Thus, a basic cumulative assessment is already being conducted at these sites. As mentioned previously, the guidance does not explain how to assess toxic interactions because quantitative methods were limited at that time. Instead, a default approach was defined under which chemicals are evaluated individually, and doses and toxic responses are assumed to be additive, providing the first U.S. EPA Program Office approaches to component-based mixture risk assessment. For independent toxic endpoints, such as different types of cancer, component risks are added. For toxicologically similar endpoints, component doses are scaled and added to give the familiar Hazard Index. The Superfund guidance also pioneered the quantitative evaluation of multiple pathway exposures with the total hazard quotient concept (see Chapter 4). Because their Hazard Index and risk addition formulas used single chemical risk values readily available from U.S. EPA's IRIS (Integrated Risk Information System) database, the

mixture assessment was feasible and continues to be widely implemented. In addition to leaving out toxic interactions, the main weaknesses of the 1989 guidance are that the screening approaches for multiple pathways are minimally described, and key details on how and when to use the total hazard quotient concept are not presented.

1.2.3. Pesticide Group Cumulative Risk Assessment. Following the passage of the Food Quality Protection Act (FQPA) in 1996, U.S. EPA programmatic guidance was developed to address a much more focused risk than that of previous site assessments. FQPA called for the estimation of health risk from combinations of pesticides with a common toxicological mode of action, from any source. The resulting cumulative risk guidance includes a modified Hazard Index formula for the mixture aspect and an aggregate risk formula that is functionally similar to the total Hazard Quotient formula in the Superfund guidance (U.S. EPA, 2002c). Sophisticated guidance was developed for evaluating toxicity data to decide which pesticides qualify for the common mode of action group (U.S. EPA, 1999a), and guidance was also developed for estimating the likely intakes from aggregate exposure from dietary and other sources based on multiple types of national or regional information (U.S. EPA, 2001a). The cumulative risk guidance was then demonstrated by an extensive risk assessment of the organophosphate pesticide group and its common mode of action, cholinesterase inhibition (U.S. EPA, 2002a). The main weaknesses of the pesticide guidance is that only the toxic effect for the common mode of action is assessed, chemicals not sharing the common mode of action are not included, and toxic interactions are not addressed.

Many site and situation health risk assessments can be adequately addressed using single chemical and single pathway evaluations. For other cases, multiple

chemicals and complex exposures will need to be evaluated jointly. Many basic cumulative risk concepts – including consideration of multiple sources, chemicals, and exposures – are in the standard guidance from the last 15 years, as these three examples illustrate. This report builds on those standard U.S. EPA guidance approaches along with new approaches so that together they provide the conceptual and procedural methodology that in many cases will be feasible and sufficient for addressing the multiple factor issues with cumulative health risk assessment.

1.3. OVERVIEW OF APPROACH TO CUMULATIVE HEALTH RISK ASSESSMENT FOR MULTIPLE CHEMICALS, PATHWAYS, TIMEFRAMES AND EFFECTS

Cumulative health risk assessment as defined in the framework (U.S. EPA, 2003a) is usually highly specific to the identified population and set of chemicals in the exposure setting. Steps can be described, however, that apply in general and that highlight the differences between cumulative risk assessment and the traditional source-based or chemical-based risk assessments performed by the U.S. EPA. Although the minimum requirement by U.S. EPA of a cumulative risk assessment is that it address joint health effects from multiple chemicals, in this report we also emphasize the community or population focus of the assessment. As described in the introduction, this report does not include all steps identified in the *Framework*, but assumes that the initial steps of Planning and Scoping and Problem Formulation have been mostly completed. The areas outlined below then apply mostly to the information gathering phase of Problem Formulation, and the subsequent steps of Analysis and Risk Characterization.

There are many situations that do not involve a population focus or that do not involve multiple chemicals and so would not need a cumulative risk assessment. This section, then, begins with a discussion of those factors that would lead to a cumulative

risk assessment, denoted here as triggers. The section then briefly describes key steps in a cumulative health risk assessment within the scope stated previously of addressing the multiples of chemicals, pathways, timeframes, and effects in a population-based setting. The activities in a cumulative risk assessment that are summarized in this section include:

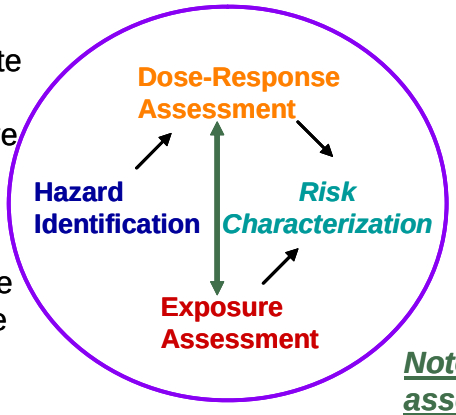
- characterizing the population or community of concern
- developing the list of chemicals
- compiling information on exposure conditions and toxicity
- identifying sensitive population subgroups and
- iterating those steps to improve the relevance of the exposure and population factors to the health risks of greatest concern.

The traditional sequence for risk assessment involves (1) hazard identification, (2) exposure assessment, (3) dose-response assessment, and (4) risk characterization. An important difference for cumulative risk assessment is that the steps no longer are conducted independently, nor in a set sequence, but involve information sharing and cross-evaluation, particularly between the exposure and toxicity assessment steps (Figure 1-5). This means that dose-response information needs to be considered during the exposure assessment, and characteristics of the exposure assessment need to be incorporated into the compiling of toxicity information and then reflected in the dose-response assessment. The exposure and dose-response assessment steps are then expected to be iterative.

One important goal of the risk assessment process is to evaluate the strength of any links between the chemical exposures to the receptor population and the

Hazard identification:
- identify possible multiple effects from multiple route exposures
- identify potential sensitive subpopulations

Exposure assessment:
- account for multiple route exposures, including fate and transport for several media
- identify potential time overlaps including fate interactions



Dose-response assessment:
- account for total absorbed dose across exposure routes over time
- assess dose-response for sensitive subpopulations

Note: Dose-response & exposure assessment are interdependent

Risk characterization:
- use metrics accounting for disparate risks, detail uncertainties associated with combining risks, discuss qualitative factors affecting risk outcomes

FIGURE 1-5

NAS Risk Assessment Paradigm Modified for Cumulative Risk, with Concepts Beyond Issues for Single Chemicals or Mixtures

information or event that triggered the cumulative risk assessment. For example, consider the case where awareness of multiple sources raises concerns over cumulative risk. The data from U.S. EPA's Toxic Release Inventory might include more than 20 chemicals, but it does not provide exposure levels or evidence that all 20 chemicals reach anyone in the population of concern. Establishing those links (e.g., between the TRI data and actual exposure) is a key part of many of the initial steps of cumulative risk assessment. In this chapter, the steps are briefly described in order to show their contributions to the risk assessment and their interconnections (Figure 1-6). More complete discussions are contained in subsequent chapters on exposure assessment (Chapter 3), toxicity assessment (Chapter 4), and risk characterization (Chapter 5).

1.3.1. Identify the Trigger for the Cumulative Risk Assessment. The initial phase of a cumulative risk assessment (planning, scoping and problem formulation) forms a systematic, iterative process that defines the risk problem to be assessed and the technical elements to be emphasized (U.S. EPA, 2003a), with problem formulation where the first analysis occurs. The main backdrop for problem formulation and initial data review is provided by the regulatory context and the particular information or technical factors (termed "triggers" in this report) that led to the decision to consider cumulative risk. Three typical triggers are shown in Figure 1-7, along with common data elements that link the triggers with the population resulting in the cumulative risk characterization. These triggers can be displayed within the preliminary conceptual model that is developed during the problem formulation phase. The identification and discussion of trigger factors in the planning stages should improve the understanding of

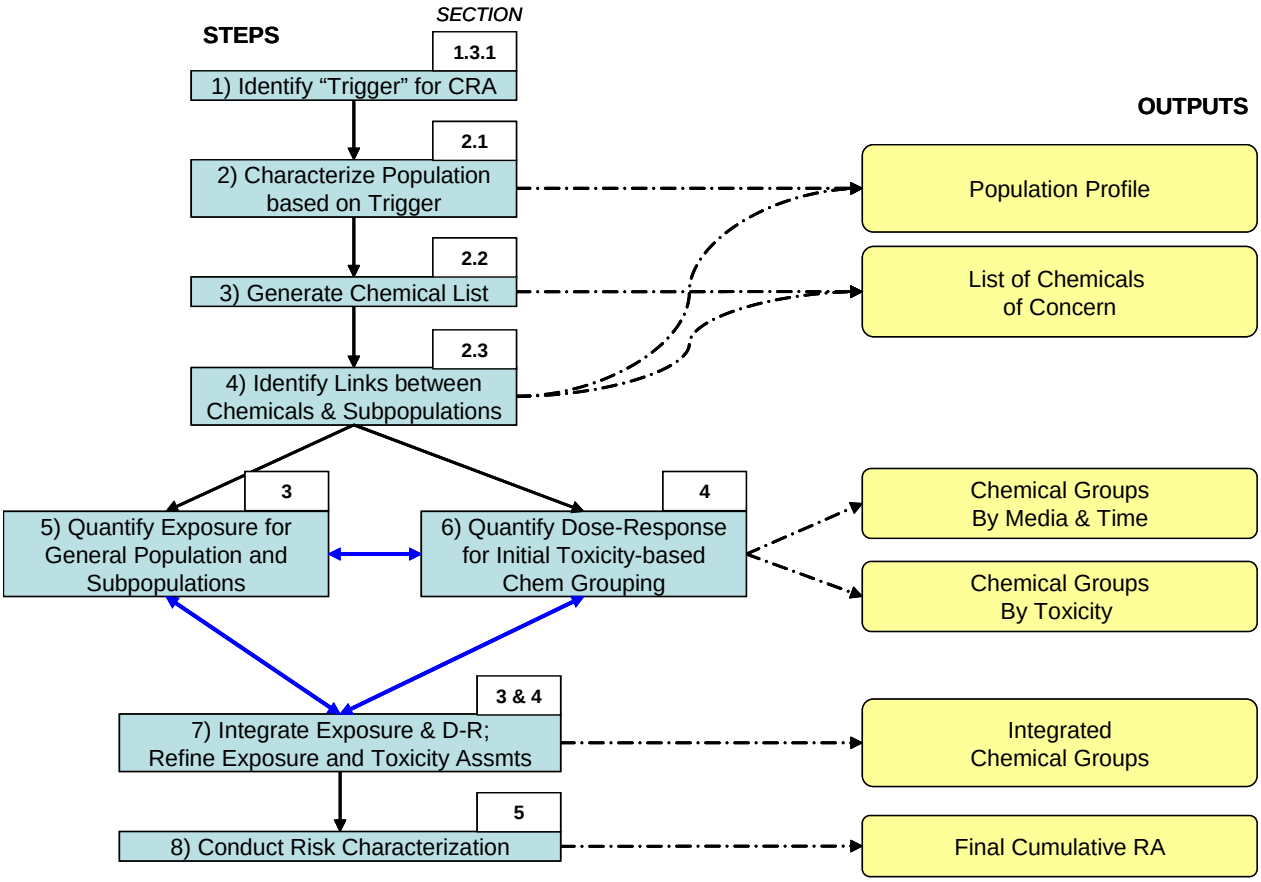


FIGURE 1-6

Key Steps in a Cumulative Risk Assessment. The interdependence of exposure and toxicity assessments is indicated by blue arrows.

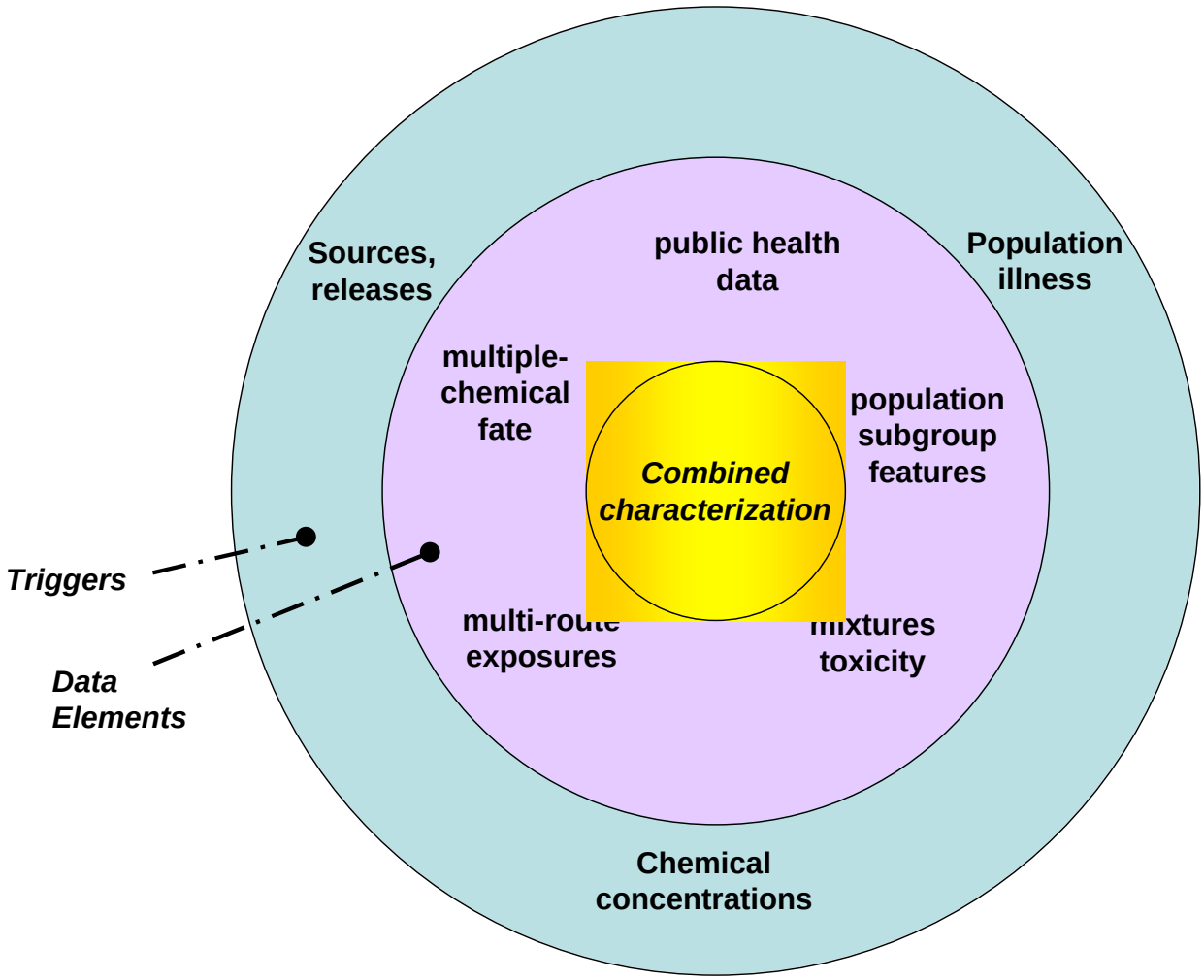


FIGURE 1-7

Information Gathering and Processing, from Common Triggers to the Resulting Cumulative Health Risk Characterization

any links between the population risk estimate, which is the result of the cumulative risk assessment, and the trigger, which initiated the risk assessment. In general, the trigger factor should be a prominent part of the final risk characterization.

1.3.1.1. Health Endpoint as the Trigger — Evidence of abnormal health effects is one of the easier triggers to understand. When serious health effects occur in a community with no clear cause, there can be a demand for an investigation. With many health endpoints, there are several possible chemical causes, so that the investigation readily becomes a cumulative risk project. For example, a cluster of leukemia cases in Woburn, Massachusetts in the 1970s triggered environmental health action, and was the inspiration for a 1995 book and subsequent movie (Durant et al., 1995). Although the eventual emphasis was on trichloroethylene exposure, the initial chemical investigation focused on several organics, while a later study investigated metal exposures (U.S. EPA, 2005a). Higher than average visits to emergency rooms and other reported unusual levels of health indicators can raise public health concerns and initiate a cumulative health risk assessment. In many cases, existence of higher than expected health effects is not easily connected to a cause, so the initial investigation might begin with a critical examination of the available health effects information. Variation in the quality of such information can be high, ranging from anecdotal articles in the press to published results in scientific journals. Having the Agency and the stakeholders gain an understanding of the details and quality of trigger information is a primary objective of the planning and scoping stage.

1.3.1.2. Chemical Concentrations as the Trigger — One of the more common initiators of a risk assessment is the detection of toxic chemicals in the environment at

unexpected concentrations, or at levels that are likely to cause toxicity. As with the health effects trigger, the variability of data quality can be high. For example, chemical levels in ambient air can have particularly high uncertainties in terms of exposure but might be easily interpreted in terms of increased health risks. High levels of urban smog, e.g., visible ground level particulates and ozone, frequently lead to public health intervention (e.g., cautions for young children and elderly to stay indoors). When combined with information on elevated chemical concentrations in soil and groundwater, it can lead to a cumulative risk assessment, such as the Cumulative Risk Initiative (CRI) for Cook County (IL) and Lake County (IN) (see U.S. EPA, 2003a, p. 32). As when health effects are the trigger, it is important to document the quality and variability of the concentration data and whether such measurements indicate possibly complete exposure pathways. The measured concentrations have even greater influence in starting a cumulative risk assessment when there are elevated concentrations of additional chemicals elsewhere, such as in food, that also impact the same population.

1.3.1.3. Multiple Sources or Release Events as the Trigger — Multiple sources of chemical contamination can be a trigger for a cumulative risk assessment, often when they are the consequence of a proposed change such as an upcoming siting decision for a new manufacturing plant. Observations of multiple uncharacterized releases can also elevate concerns. For example, repeated discharges from multiple outfalls into streams have led to actions by Georgia Riverkeeper groups, ranging from lawsuits to scientific sampling of the water and biota (Richardson, 2004). A proposed increase of multiple sources is often a stronger motivation for a cumulative risk assessment when the potentially exposed population includes known susceptible

subgroups. One of the first activities is to determine all sources with potential exposure to the population of concern, particularly sources with chemicals similar to those in the trigger sources. For example, an investigation into possible pesticide drift to a residential neighborhood from nearby farms could also estimate concurrent exposures from household use of similar pesticides by residents of the neighborhood of concern.

1.3.2. Characterize the Community and Population Based on the Trigger. The population characterization usually would include a physical description of the study area and a demographic description of the population in that study area. The study area could be a political unit, such as that defined by a county or city boundary, or could be delimited by geographical features, such as a lake and surrounding watershed. The population could be a neighborhood or the community in an entire city or could be the public using a resource, such as a lake. The population description would also include sensitive or susceptible subgroups based on increased exposure or vulnerability. Often the definition of the population and study area could be influenced by the trigger factor that initiated the risk assessment. Because a cumulative risk assessment is population focused so that all relevant exposures and effects are considered, as the potential exposures and toxic effects are further investigated, the population characterization will be refined.

1.3.3. Generate Initial Chemical List. The U.S. EPA *Framework for Cumulative Risk* (U.S. EPA, 2003a) distinguishes cumulative risk assessment from the traditional risk assessments by its population focus. Consequently, once the initial population description is complete, including the boundaries of the study area, information on chemical releases and environmental concentrations are evaluated in light of the

identified population to develop the initial list of chemicals of concern. Existing U.S. EPA approaches for exposure assessment are likely to be sufficient for this step. Partly because of stakeholder involvement in the cumulative risk assessment, this initial chemical list is likely to be closely tied to the trigger factor. The influence of the trigger factor is discussed in more detail in the exposure assessment chapter.

1.3.3.1. Use Program and Regional Office Procedures — Determination of chemicals of concern is covered in several guidance documents from the U.S. EPA Program and Regional Offices (see Appendix A). For exposures by multiple media, the chemicals might need to be identified using approaches from several Programs or using guidance from U.S. EPA's Office of Research and Development (ORD). The initial chemical list should be overly inclusive so that potential interactions from joint exposures and joint toxicity can be evaluated in later steps of the assessment. For example, chemicals that might be screened out in a single chemical assessment because their Hazard Quotient (HQ) was less than 1 might be retained in a cumulative assessment unless their HQ was less than 0.1, in order to allow for potential dose additivity or interactions.

1.3.3.2. Identify Chemicals Related to the Trigger Factor — The three types of trigger factors in this report have only subtle differences in their influence on the chemical list. When health endpoints are the trigger, the preliminary list of chemicals could include any that have been shown in human or animal studies to cause or contribute to those health effects. When environmental concentrations or sources are the trigger, the preliminary chemical list could be at first restricted to those measured or likely to be in the emissions. Chemicals known to be similar to or toxicologically

interactive with those on the first list might then be added if their exposure to the population defined in the step in Section 1.3.2 is considered plausible, such as similar chemicals in food. That determination of potentially interactive chemicals should also consider multiple endpoints for each chemical, not just the critical effect used to define the IRIS risk values. In any case, the resulting list of chemicals is preliminary and perhaps most useful in refining the population description by identifying subgroups that could be sensitive to chemicals on this list.

1.3.4. Identify Links between Chemicals and Subpopulations. Once the general receptor population has been identified and characterized and the preliminary chemical list exists, the next step is to attempt to link those chemicals with population groups, including sensitive population subgroups in the defined population of concern. Population groups can be of heightened sensitivity to toxic chemicals because of higher exposure or increased vulnerability. Higher exposures can often be estimated by occupational and lifestyle information and have been addressed by U.S. EPA for some time. One difference for cumulative risk assessment is that elevated exposures can include the combined exposure to multiple toxicologically similar chemicals, e.g., chemicals in workplace or lifestyle exposures (e.g., food sources) that are not on the preliminary chemical list. Because of the population focus and stakeholder involvement, cultural or other lifestyle factors might be identified by stakeholders that could suggest additional sources of chemicals or exposure levels of significance that could then lead to additional sensitive population subgroups. Vulnerability can be more complex, ranging from existing disease (e.g., hospital patients) to genetic predisposition (e.g., for some lung cancers) to socioeconomic factors (e.g., access to health care). Vulnerability

is discussed in some detail in the next chapter but many issues are poorly understood and are foci of current research.

The chemical list should then be combined with the description of likely sensitive population subgroups. This information could be arranged in several ways. For example, a table could list the chemicals ranked by the strength of their link to the trigger factor. For example, chemicals linked to population subgroups that are also identified in emissions from the multiple sources (the trigger factor) would be listed first. Chemicals linked to sensitive subgroups of the population of concern could be further described by an indicator of the strength of that link (e.g., based on human data or extrapolated from experimental animal studies) and the size of the sensitive subpopulation. Chemicals could be further identified by their potential for joint exposure (e.g., by multiple routes) or joint toxicity with other chemicals on the list. Any chemicals that could not be adequately evaluated (e.g., lack of toxicity information), or that initially were deemed unlikely to pose significant health risks, could be placed on a "watch list" pending further analysis during the iteration of the exposure and toxicity assessment steps.

1.3.5. Quantify Exposure for General Populations and Subpopulations. The initial exposure assessment is next. Up to this point, no actual exposure assessment has been performed, only a listing of chemicals. Extensive U.S. EPA guidance is available for conducting assessments for the three major routes of exposure: dermal, oral, and inhalation (see Chapter 3 for details and citations). For multiple sources and pathways, detailed exposure guidance exists for combustor emissions (U.S. EPA, 1998a) along with programmatic guidance on Superfund sites and multiple pesticide exposures (U.S.

EPA, 1999a,b). In general, the assessment might need to reflect guidance across several Programs or from ORD. For example, general exposure guidance and information on exposure factors are available from the National Center for Environmental Assessment (U.S. EPA, 1992a, 1997c, 1998a, 2002i), guidance on aggregate exposures to pesticides is available from the Office of Pesticide Programs (U.S. EPA, 1999e, 2001a), guidance on exposure from hazardous waste combustion facilities is published by the Office of Solid Waste and Emergency Response (OSWER) (U.S. 2005d), and dermal exposure to soil is covered by the supplemental OSWER guidance (U.S. EPA, 2004a).

Quantification of exposure for cumulative risk assessment should begin with a clear definition of the population and study area (see Section 1.3.2) so that the assessor can identify all existing and future completed pathways. The assessment should also identify the relevant exposure factors, with particular attention to unique factors for the sensitive subpopulations. Once the exposure is characterized for the population of concern and its sensitive subpopulations, the next step is to attempt to simplify the combinations of chemicals, pathways, and timing (including duration and intermittency of exposure) by grouping the chemicals according to media or pathway, and according to timing.

Any issues that cannot be quantified should be described qualitatively regarding their relative importance to the population exposure and for possible future quantification should information become available. Information from the dose-response assessment would be useful in this evaluation of those unquantified issues, particularly in terms of exposures of sensitive subpopulations.

1.3.6. Quantify Dose-response for Initial Toxicity Grouping. The focus of toxicity assessment regarding cumulative risk revolves around timing issues of exposure and toxicity. The grouping resulting from the exposure quantification (by timing, media, pathway) should then be further evaluated in terms of toxicological timing factors: toxicological overlap of internal dose, kinetics interactions, toxicodynamic interactions, and persistence of effects (see Chapter 4 for details and additional references). Simultaneous exposures are the ones most often evaluated for potential joint toxicity, but sequential exposures can also result in joint effects. Initiators and promoters of cancer and delayed or persistent toxicity are examples where potential joint toxicity could occur from exposures at different times.

Chemicals previously put on the "watch list" could be reexamined in this step through consideration of the potential or expected toxicity at the estimated exposure levels. Toxicologic interactions could be further considered for the watch list chemicals, perhaps via structure-toxicity relationships or other similarity procedures, as could interactions involving characteristics of the sensitive subpopulations. An example of the latter interaction is nutritional deficiencies enhancing toxicity of some metals (U.S. EPA, 2004b). Any dose-response or other toxicity issues that cannot be quantified should be described qualitatively, especially regarding importance to potential health effects in the sensitive subpopulations.

1.3.7. Integrate Exposure and Dose-response Information. In this final analysis step, the exposure assessment should interface with the dose-response assessment in order to refine the information on joint exposures of main toxic significance and to identify timing issues of most concern regarding increased toxicity. Any matches of

toxicity overlaps (toxic interactions or persistent effects) with exposure overlaps should be highlighted for consideration of improvements in the exposure information. The refined exposure and toxicity characterizations and the resulting initial risk estimates, the products of this step, are the main inputs to the risk characterization.

1.3.8. Conduct Risk Characterization. A risk characterization is usually described in U.S. EPA guidance as having two parts: an integrative analysis, which contains the risk estimates and can be highly technical, and a risk characterization summary, which has minimal jargon and focuses on recommendations and uncertainties. As mentioned previously, the sequence is slightly different in the *Framework for Cumulative Risk* (U.S. EPA, 2003a), where the initial risk estimates are developed in the previous steps because of the interplay and coordination of the exposure and toxicity assessments. The cumulative risk characterization can also differ from a traditional risk characterization in a number of ways (detailed in Chapter 5) that are often caused by missing data or a lack of understanding of the various multiples and their interactions. Some of the more important differences are:

- Recommendations could be multivariate, i.e., the assessor might not be able to identify a single chemical, pathway, or critical effect that drives the risk.
- Recommendations might be based on grouping of chemicals, pathways and effects, but such grouping can be subjective.
- Uncertainty analysis might be predominantly qualitative because of the need for numerous defaults, e.g., for addressing interactions and multiple effects.
- Time dependence of exposure and mixture composition might be addressed by surrogates (e.g., annual averages) or simplified factors (e.g., index chemical concentration) resulting in complex analyses and unknown information gaps.

The cumulative risk characterization will also differ from more common single chemical and source-based assessments by its focus on the population of concern and its sensitive subgroups.

2. INITIAL CHARACTERIZATION OF THE POPULATION AND CHEMICALS OF CONCERN

Once the trigger factor has been described, the next steps involve defining the population of concern and its study area, the chemicals of concern, and links between environmental chemical exposures and sensitive subgroups of the population. The steps in this chapter then form the initial collection and organization of information to focus on the cumulative aspects of the risk assessment, shown as steps 2-4 in Figure 1-6. Sections 2.1 and 2.2 describe the preliminary evaluations of population and exposure information including the influence of the trigger factor on those evaluations. Section 2.3 describes the linking of population and exposure information to identify any subgroups of that population that would be sensitive to effects from those exposures and the use of conceptual models to help organize the information and analysis. As shown in Figure 1-6, the expected product of the linking step is a refined characterization of the population and its sensitive subgroups along with a refined list of chemicals of concern. Subsequent steps in Chapters 3-5 will involve more detailed evaluation and quantification of exposure, dose-response, and then cumulative health risk.

2.1. INITIAL DESCRIPTION OF THE POPULATION

In contrast to the source-based approach that begins with releases and addresses all populations impacted by those releases, a receptor-oriented study could begin by defining the population group of interest, and addressing all sources impacting that population. The population group could be determined by geographic, demographic, or other criteria. This population group can be identified from the findings

of a recent exposure study or might simply reflect locations of concern to U.S. EPA or certain stakeholders, which could range from school yards or parks to homes and sacred lands. Under this orientation, the exposures are traced back to evaluate all pathways by which a given subpopulation could be exposed to a variety of chemicals, which could include diet and other lifestyle contributions. As described in the Agency's framework document, this approach is often applied to community-based cumulative health studies (U.S. EPA, 2003a). It can also play a role in other applications that are more often source-based. For example, the assessments for contaminated sites could use a population-based approach to address a specific group for whom unique exposure or vulnerability/susceptibility issues are of concern (see Chapters 3 and 4). The analysis plan for a cumulative health risk assessment could then reflect a combination of source- and receptor-based approaches.

2.1.1. Preliminary Characterization of the Population Based on the Trigger. The initial population characterization usually would include a description of the study area and the population in that study area. The trigger factor could influence whether the study boundary or the population is defined first. Consequently, the initial population of concern could be the community in an entire city or county, especially any identified sensitive or susceptible subgroups of that population or community, or it could be those in frequent contact with a geographic area, such as a park or lake. In general, the trigger factor should be a prominent part of the final risk characterization. Sometimes the stakeholders and U.S. EPA agree after further evaluation that the trigger factor has been determined to be of lesser significance, and that another factor will be the key motivation for continuing the cumulative risk assessment. The initial description of the

study area and population of concern should then be considered preliminary and subject to change during the course of the risk assessment.

2.1.1.1. Population Defined by the Health Endpoint — If a population group is associated with the trigger health effect, then that subgroup automatically is in the initial population of concern. For example, if the trigger is an increased absence from school for children 12 years and younger because of respiratory problems, then that group of children forms the initial population of concern and could be deemed the sensitive subgroup as well. Because cumulative risk assessment can include multiple endpoints, the population could be initially defined in broad and somewhat vague terms, with refinement following the later steps when links are determined between the trigger health endpoints (as well as other endpoints) and chemical exposures.

2.1.1.2. Population Defined by Chemical Concentrations — Monitoring locations where elevated chemical concentrations were detected can define the bounds of the study area. If transport is plausible for those chemicals, then the study area and population can be much larger than the initial contamination zone. Chemical concentrations limited to specific resources or geographic features can lead to a study population defined by those with likely access to that resource or location. Contamination of a recreational lake might lead to the population defined as those known and potential users of the lake. At this stage, the identification of sensitive population subgroups might only be based on known sensitive groups in the defined population. Common example sensitive groups are children, pregnant women, and the elderly.

2.1.1.3. Population Defined by Multiple Sources — When multiple sources are the trigger factor, exposures have not yet been estimated. The initial boundaries of the population of concern might then be roughly defined by possible dispersion characteristics of existing and possible future emissions, as well as populations with possible future exposures. The trigger sources could initially be considered in isolation. As the assessment proceeds, the refinements would consider all sources so that the trigger sources might be evaluated both for their incremental population risk as well as in the context of risk from other sources.

2.1.2. Characteristics of Vulnerable Subpopulations. U.S. EPA's *Framework for Cumulative Risk* (2003a) adopts "vulnerability" concepts that encompass the topic of receptor characteristics. Four areas are articulated where "human and biological ecosystems, communities, and populations may be vulnerable: susceptibility/sensitivity, differential exposure, differential preparedness, and differential ability to recover." Given this context, receptor population characteristics may include diverse factors such as genetic susceptibility, age, stress, disease state, economic status, ethnicity, health status, proximity to sources, activity patterns, etc. Factors that affect a population's vulnerability should be considered in the conduct of a cumulative risk assessment. Risks should be calculated separately for populations with specific receptor characteristics to yield more realistic estimates of the health risks from cumulative exposures.

Studies in the literature suggest that certain receptor characteristics might contribute to the toxicity caused by chemical mixture exposures. For example, Perera et al. (2004) present molecular epidemiologic evidence that combined exposures to

environmental levels of two mixtures, polycyclic aromatic hydrocarbons (PAH) and environmental tobacco smoke (ETS), in New York City adversely affected fetal development in inner city minorities. In this case, minorities were thought to be differentially exposed to ETS, increasing their susceptibility to environmental levels of PAH. There were no PAH-related developmental effects in the absence of ETS. The results of this study revealed an unexplained ethnic difference in that "mean birth weight and head circumference were lower and there was greater variability in these outcomes among African Americans than in Dominican infants." For a cumulative risk assessment, a factor such as differential exposure to ETS should be taken into account when evaluating an environmental mixture.

Example of Pesticides and Farmer Characteristics
(Text Box 2-1)

A large, prospective epidemiologic study, The Agricultural Health Study, is an ongoing effort to evaluate health effects in agricultural cohorts in North Carolina and Iowa from pesticide exposures (Alavanja et al., 1996). On aspect of this study is to examine the impacts of lifestyle, cultural, ethnic and genetic factors on the health of farmers in conjunction with pesticides exposures, making it an important contribution to the literature on cumulative risk assessment. Results from this study will likely be published for years to come, but a few articles are already available. Current results include:

- Increased prostate cancer risk for study subjects with a family history of prostate cancer (Alavanja et al., 2003).
- Increased prostate cancer risk for applicators over 50 years in age who used chlorinated pesticides (Alavanja et al., 2003).
- Identification of poor financial condition of the farm, limiting the purchase of safety equipment, as a significant risk factor for acute effects from high pesticide exposure events (Alavanja et al., 2001).
- Higher pesticide exposures and more pesticide-related health effects in white farmers than in black farmers, which may be explained by farm characteristics or economics (Martin et al., 2002).
- Association of specific pesticides (i.e., paraquat, parathion, malathion, chlorpyrifos, thiocarbamate) with respiratory symptoms of farmers (Hoppin et al., 2002).

In the assessment of rural communities, the literature suggests that impacts from exposures to mixtures of pesticides should be evaluated from a cumulative risk perspective (see Text Box 2-1). Another example involving multiple route exposures to 24 organophosphorus (OP) pesticides (U.S. EPA, 2002a) is discussed in Section 4.4.2.

2.2. INITIAL ASSESSMENT OF EXPOSURE DATA

As mentioned previously, the need to conduct a community-based cumulative risk assessment could be initiated by any of the three triggers (i.e., multiple sources/release events, elevated chemical concentrations, or a concern about population illness) individually or in combination (Figure 2-1). This section provides a general description of the types of chemical information likely available and initially needed in the early part of the exposure assessment process and its dependence on the trigger factor. It also discusses specific population data that need to be collected initially in order to conduct the exposure assessment. Specific approaches to the cumulative exposure assessment are discussed in Chapter 3.

2.2.1. Initiating the Exposure Assessment when Health Endpoint is the Trigger.

When an increased incidence of health endpoints triggers an assessment, the initial goal of the investigation is to determine if environmental chemicals/stressors present in a community are linked in some way to those health endpoints. These types of analyses are similar to primary epidemiologic investigations, such as that conducted to determine why there are elevated rates of female breast cancer in a region (Aschengrau et al., 2003; Paulu et al., 2002). Text Box 2-2 provides an example of an illness trigger

Example of Illness Trigger from Pesticide Incident
(Text Box 2-2)

Information reported to health officials	5 children with abdominal pain. 2 days later, additional 2 children with all 7 showing respiratory arrest, symptoms of organophosphate (OP) poisoning. 2 children died. All 7 were siblings.
Setting observations	Household, recently sprayed with unknown insecticide by adult resident.
Investigative discovery	Illegal pest-control application of methyl parathion inside home at 3x concentration used in agricultural spraying (this organophosphate pesticide is only intended for outdoor use)
Specific chemical toxicity	Affects central nervous system: nausea, dizziness, headache, vomiting, high levels can be fatal
Exposure assessment	Samples from sprayer, food, water, air. Biomonitoring (fluid samples) to identify people exposed (multi-pathway) & focus response actions
Risk management action	Decontamination of house and increased publication of dangers of inappropriate OP use.
Source	CDC (1984).

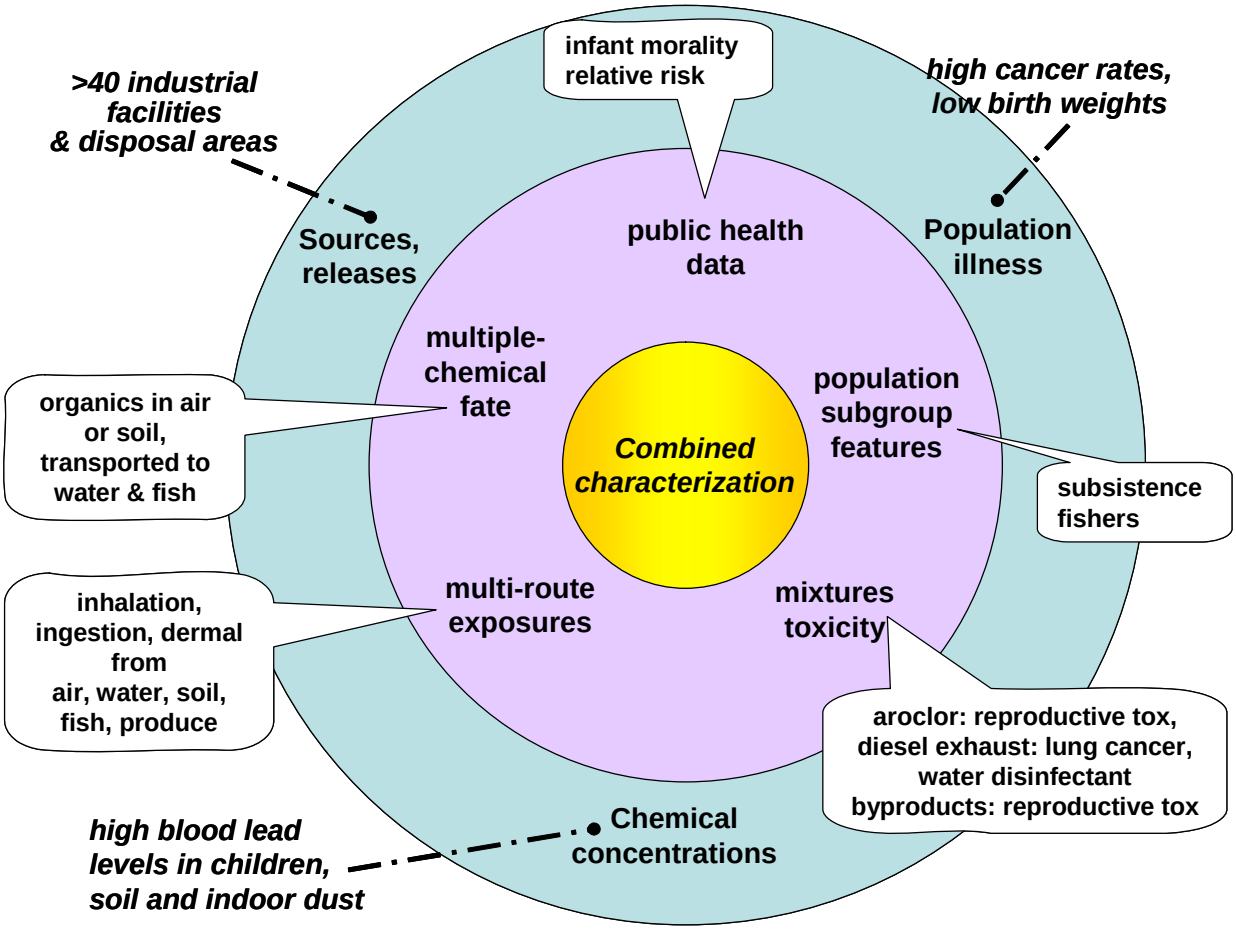


FIGURE 2-1

Example Triggers and Data Elements for Cumulative Risk Analyses

initially attributed to general organophosphate (OP) poisoning and later focused to exposure to a single pesticide. Health registries can serve as important resources for evaluating cumulative risks from environmental exposures, and a number already exist. For example, most states maintain cancer registries, as do national organizations, e.g., the Centers for Disease Control and Prevention. A number of birth defect registries also exist (over 30 states), but the quality of most data is considered inadequate for an effective tracking program (EHTPT, 2000), particularly regarding implications of environmental exposure to multiple chemicals.

When an increased incidence of health endpoints triggers an assessment, the initial phase of the data gathering involves a collection effort that focuses on identifying chemicals (individually or in groups) that are known to cause the effect in humans or some animal species (e.g., effect identified in rodent bioassays). Although Table 2-1 identifies a number of illnesses that are linked to environmental contaminant exposures, chemical combinations and exposure conditions can be highly situation-specific, so that identification of chemicals and chemical mixtures related to specified health effects is typically initiated through a literature review. The literature review should not be limited to primary effects but should consider secondary effects as well; for example, the RfD of a chemical may be based on hepatotoxicity (i.e., hepatotoxicity was the most sensitive endpoint), but the literature review may show that the chemical is also a potential reproductive toxicant at doses higher than the LOAEL. The initial data collection for the exposure analysis may be conducted in conjunction with the dose-response and toxicity analysis, so that specific chemical mixtures of concern (given the health endpoints) are identified, and chemicals with known toxic interactions can be considered for additional

1

TABLE 2-1
Examples of Illnesses Linked to Multiple Environmental Factors[a]

Illness/ Health Effect	Hypothesized Causes/ Epidemiological Links	Associated Levels	Remarks	Reference
Acute mylogenous leukemia (AML)	Benzene, ionizing radiation, alkylating agents, and topoisomerase inhibitors.	Increased incidence of leukemia observed in lifetime occupational studies at 10-50 ppm benzene and higher. However, these levels exceed the U.S. occupational 8-hour standard of 1 ppm for benzene in air so are unlikely to occur.	Benzene is present in gasoline, automobile exhaust, and cigarette smoke, the latter of which also emits radiation. AML is also a secondary cancer after treatment for primary cancers, and links between AML and genetic (inherited) conditions and viruses have also been established.	Hricko, 1994; U.S. EPA, 1997b
Allergic contact dermatitis	Nickel and chromium	The European Union (EU) has prevented sale of nickel-containing objects that release over 0.5 µg nickel/cm^2 skin per week.	Delayed skin inflammation and rash can occur; nickel is commonly used in some jewelry. Note that the EU nickel limit might not protect all sensitized persons (no similar U.S. limit has been placed on nickel content in jewelry or other consumer products).	Nickel Institute, 1999; Amdur et al., 1993
Asthma	Particulates, including high molecular weight (HMW) allergens (polymers or proteins of animal, plant, bacterial, or fungal origin in range of 20-50 kilodaltons).	A 14% increase in emergency room visits due to asthma was associated with very fine particulate matter (PM2.5) averaging 12 µg/m^3 (for 15 months).	Asthma is exacerbated by both indoor and outdoor pollutants as well as allergens. Correlations have been observed between asthma and sensitivity to cockroaches and to HMW allergens.	Norris et al., 1999; O'Connor and Gold, 1999

2

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TABLE 2-1 cont.

Illness/ Health Effect	Hypothesized Causes/ Epidemiological Links	Associated Levels	Remarks	Reference
Blackfoot disease	Arsenic	Observed in people consuming well water with 170 µg/L arsenic and higher. (This concentration is much higher than the U.S. drinking water standard of 10 µg/L.)	Blackfoot disease, a severe form of arteriosclerosis, is a vascular complication of arsenic exposure. Blackfoot incidence increases with age.	U.S. EPA, 2005c; Amdur et al., 1993
Liver cancer	Many (>100) chemicals, including chlorinated solvents, aflatoxin, and animal products (meat, eggs).	For aflatoxin (which can be found in peanut butter), Americans could consume up to 0.15-0.50 µg/day. Organic solvents are ubiquitous at low levels in urban air and hazardous waste sites.	Causes of liver cancer are many and varied; this organ is the most common site for mutagens and non-mutagens. To illustrate for aflatoxin, effects can be confounded by hepatitis B infection, which is endemic in areas where high intake is common.	NTP, 2002; Gold et al., 2001; CPDP, 2004; ATSDR, 2001
Lung cancer	Dozens of chemicals, including those in cigarette smoke, and radon.	Average U.S. radon levels of 4.4 to 11 becquerels/m^3.	Tobacco smoke is the leading cause of lung cancer. Lung cancers increase multiplicatively when radon is combined with cigarette smoking.	NTP, 2002
Neurological damage/ reduced intelligence quotient (IQ)	Lead in lead-based paint; mixtures of polychlorinated biphenyls (PCBs) and dioxins; fetal irradiation.	An increase in blood lead levels from 10 to 30 µg/dL resulted in an IQ reduction of 4 to 5% (4.4 to 5.3 points) in 7-year-old children	People can be exposed to lead via many sources, e.g., paint, soil and dust, drinking water, food, occupational exposure, burning candles with lead wicks, and hobbies.	Baghurst et al., 1992; NYSDOH, 2003; Birnbaum, 1995

TABLE 2-1 cont.

Illness/ Health Effect	Hypothesized Causes/ Epidemiological Links	Associated Levels	Remarks	Reference
Parkinson's Disease and Parkinsonism (which might be reversible)	Many pesticides, including organophosphates, organochlorines, carbamates, various herbicides and household fumigants; and copper and manganese.	Increases in Parkinson's disease has been observed in connection with chronic pesticide exposures. Reversible Parkinsonism has been seen following acute pesticide exposures. One occupational study found 6% of workers exposed to >5 mg/m^3 manganese exhibited acute Parkinson's symptoms.	Risk factors have been identified for people in farming areas, especially those with a history of pesticide exposure. Some who die of Parkinson's have higher levels of organochlorine pesticides in brain tissue than the general population. Idiopathic causes account for >85% of all cases; suspected links exist to MPTP,[b] organomercury, encephalitis, major tranquilizing drugs, carbon monoxide or disulfide poisoning, and frequent head injuries.	Hileman, 2001; Feldman, 1992; Gorell et al., 1999

[a] This table illustrates illnesses or health effects that have been linked with various environmental exposures (some lifestyle factors are also shown) and that might trigger a cumulative assessment concern because of the number of possible chemical causative agents and their likely joint toxicity.

[b] MPTP is the drug 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

exposure measurements and analysis. In conjunction with dose-response analyses, the analysis should examine if there are specific subpopulations sensitive to the identified health effects or whether chemical exposures could exacerbate an existing condition in potentially sensitive individuals, based on toxicokinetic or toxicodynamic information. In summary, the goal of this first step is to determine the pollutants of concern (either individually or in groups) that have been linked to the trigger effect and similar health effects, and the combinations of subpopulations and pollutants of concern that might require more detailed exposure assessement because of higher exposure and/or enhanced toxicity in those subpopulations.

2.2.2. Initiating the Exposure Assessment when Elevated Chemical Concentrations are the Trigger. When increased chemical concentrations trigger a risk assessment, the initial goal of the investigation is to determine if those concentrations could result in exposures that could cause potentially important health effects in the community, including secondary health endpoints and toxicological interactions. The initial phases of these types of analyses are similar to the steps undertaken in traditional risk assessment analyses such as those presented in the *Risk Assessment Guidance for Superfund* (U.S. EPA, 1989a). From an exposure perspective, following identification of the chemicals of interest, aspects of which are discussed next, such analyses will determine the spatial bounds of the assessment, examine the fate of the identified pollutants, determine whether (and which) individuals in the community are or could be exposed and quantify such exposures. These are standard components of an exposure assessment.

When increased chemical concentrations trigger an assessment, the initial phase of the data gathering focuses on identifying the chemicals present in the community, documenting the locations of these elevated concentrations (existing data on the locations of these elevated concentrations could be supplemented with information provided by stakeholders about the locations of previous polluting operations practiced in the community) and examining the health effects associated with these chemicals. In conjunction with dose-response analyses, the primary and secondary health effects associated with the individual chemicals or groups of chemicals should be identified. Because a cumulative assessment is being initiated, the analysts should evaluate whether there are other chemical exposures that could be occurring in the community that could increase the toxicity of the chemicals known to be at high concentration. This could involve an examination of potential sources of pollution in the community (the Toxic Release Inventory (TRI) reports on pollutants typically released from these sources) followed by monitoring of related environmental media. Other U.S. EPA documents (e.g., *Human Health Risk Assessment Protocol for Hazardous Waste Combustion Facilities* [U.S. EPA, 2005d]) can be of help in identification of the types of compounds typically released from a source class. In summary, the goals of this first phase are (1) to identify likely multichemical exposures to those chemicals with high environmental concentrations, (2) to characterize the primary and secondary health effects potentially associated with those chemicals, and (3) to determine if there are other pollutants (either individually or in groups) that should be monitored in other media (e.g., household pesticide use) because of their influences on exposure or because they produce similar health effects .

2.2.3. Initiating the Exposure Assessment when One or More Sources is the Trigger. When one or more sources trigger an assessment, the initial goal of the investigation is to determine if the chemicals released from those sources could cause exposures high enough to cause important health effects in the community. For example, releases of highly volatile chlorinated solvents into ambient air are usually only considered significant for populations close to the source as they disperse rapidly (ATSDR, 2001). With multiple sources, of most importance for cumulative risk assessment is the determination of which chemicals from those sources will reach the population of concern. Sources of chemical pollutants include (1) point sources, such as industrial and commercial boilers, electric utility boilers, turbine engines, wood and pulp processers, paper mills, industrial surface coating facilities, refinery and chemical processing operations, and petroleum storage tanks and (2) area sources such as piping leaks, industrial wastewater treatment ponds, quarry operations, tank farms, and on-road and off-road vehicles. The initial phases of these types of analyses are similar to the steps undertaken in traditional risk assessment analyses that analyze single sources such as those presented in the *Risk Assessment Guidance for Superfund* (U.S. EPA, 1989a) and those presented in the *Methodology for Assessing Health Risks Associated with Multiple Pathways of Exposure to Combustor Emissions* (U.S. EPA, 1998a). Following identification of the source(s) and chemicals of potential interest, aspects of which are discussed next, such analyses will

- characterize the source(s) by compiling basic facility information
- determine the spatial bounds of the assessment
- examine the fate of the released pollutants

- determine whether (and which) individuals in the community could be exposed and
- quantify such exposures.

These steps are standard components of an exposure assessment.

When one or more sources trigger an assessment, the initial phase of the data gathering focuses on identifying the types of chemicals released from those sources, including potential future releases, that could impact the community. There may be different types of sources involved, so that exposure assessment guidance from several U.S. EPA Program Offices might have to be consulted. Most Agency Program Offices have procedures for determining the important chemicals released from different point sources of concern. For example, Chapter 2 of the draft *Human Health Risk Assessment Protocol for Hazardous Waste Combustion Facilities* (U.S. EPA, 2005d, Volume 1) presents an approach for identifying compounds of potential concern that are emitted from hazardous waste combustors. In addition to the chemicals released from the identified sources, the analyst may wish to examine other sources, including nonpoint sources, of specific pollutant exposures to the community. In addition, in conjunction with dose-response analyses, the primary and secondary health effects associated with the individual chemicals or groups of chemicals need to be identified so that the exposure assessment can group those chemicals in the identified sources that jointly influence the same health effects. In summary, the goal of this first phase is to determine those pollutants (either individually or in groups) from the identified sources that are of concern for the community because of likely co-exposures at concentrations of toxicological significance.

2.2.4. Summary. During the initial assessment step, approaches are available to focus on what emissions sources, chemicals or population locations should be included in the cumulative assessment and what chemicals should be evaluated together. In evaluating which chemicals are of concern for a community, it is useful to consider the specific triggers for the cumulative assessment and any issues that might be of special interest to the stakeholders. Although more detailed approaches to exposure assessment are discussed in Chapter 3, some insight on focusing the assessment can be gained from criteria commonly used for retaining or excluding chemicals. The chemical selection criteria recommended by Agency Program Offices typically include:

- chemical toxicity
- mass of chemical released or mass of chemical present in media
- the potential for physical or chemical interactive effects with other chemicals in the area and with other media
- the tendency to persist, bioaccumulate, and/or be transported between environmental media
- the potential for relatively high exposures to sensitive populations.

In addition, for a population-focused cumulative risk assessment, the chemical selection criteria should also include:

- the possible contribution to induction of health effects that exist at relatively high levels in the study population
- likelihood of exposure to the population of concern
- potential for overlapping exposures (times and routes) to toxicologically similar or interacting chemicals.

Depending on the community and the trigger, these criteria could be adapted or augmented.

2.3. LINKING THE LIST OF CHEMICALS OF CONCERN TO THE POPULATION PROFILE THROUGH A CONCEPTUAL MODEL

Following the initial data collection, the chemicals and endpoints of concern should be evaluated for linkages to sensitive population subgroups in the community or the population being assessed. The first goal of this phase is to determine if any of these chemicals or subpopulations are present in the community. In addition to identifying and examining chemical releases from local sources, the cumulative assessment could include an examination of possible regional and national sources of these potentially hazardous chemicals. The assessment could also examine if there are unique exposure sources or pathways for the sensitive populations identified. The analysis could also examine the spatial relationship between the identified sources and residences, sources of food, playgrounds, schools, etc. to identify individuals or groups of people in the community who might be affected. Other community-based methods highlight the importance of community involvement in the risk assessment planning process (U.S. EPA, 1997a).

One of the desired outputs from the planning and scoping phase of cumulative risk assessment (U.S. EPA, 2003a) is a conceptual model. This model provides both a written and visual representation of the structure and dynamics of the system being assessed that is subsequently converted into an implemented approach (Suter, 1999; Suter et al., 2003). Conceptual models typically identify the links between main system components, i.e., the sources, chemicals, exposure pathways, exposure routes, subpopulations, and health endpoints that will be analyzed (Suter, 1999). Conceptual models should identify what sources, endpoints, and processes are included and which are excluded, and what assumptions are being made. Once the initial exposure and

population descriptions are completed, a preliminary conceptual model can then be developed jointly by the exposure and dose-response analysts, to ensure that all relevant exposures and endpoints are included. During the analysis phase of the exposure assessment, the preliminary conceptual model is refined by incorporating further information gained during the analysis steps (Chapter 3, Section 3.3).

Some key elements of a conceptual model for evaluating cumulative exposures are shown in Figure 2-2. This figure depicts sources, processes, receptors, and flows between them, but in general terms, showing how the same model components can apply beyond the scope of this report to include other receptors and effects. Particularly for cumulative risk assessments that consider several multiples (e.g., sources, chemicals, pathways, effects), such as at a contaminated site, it is better to develop a hierarchy of conceptual models instead of trying to represent the multiples in one model (Suter, 1999). In the case of a Superfund site, soils are typically contaminated, and contaminants are also often found in surface water, groundwater, and indoor air of buildings on or surrounding the site, so a first level conceptual model can be a fairly simple picture (Figure 2-3). As described in the U.S. EPA *Risk Assessment Guidance for Superfund* (U.S. EPA, 1989a) and from a cumulative exposure assessment perspective, unique exposures in populations living near this site might require detailed evaluation. In the next chapter, Figure 3-2 displays in more detail the components of a cumulative exposure assessment along with primary exposure routes for potential receptors, suggesting possible populations of elevated exposure, such as individuals who consume large quantities of local fish (recreational exposure to surface water). More detailed conceptual models and diagrams for cumulative exposure are presented

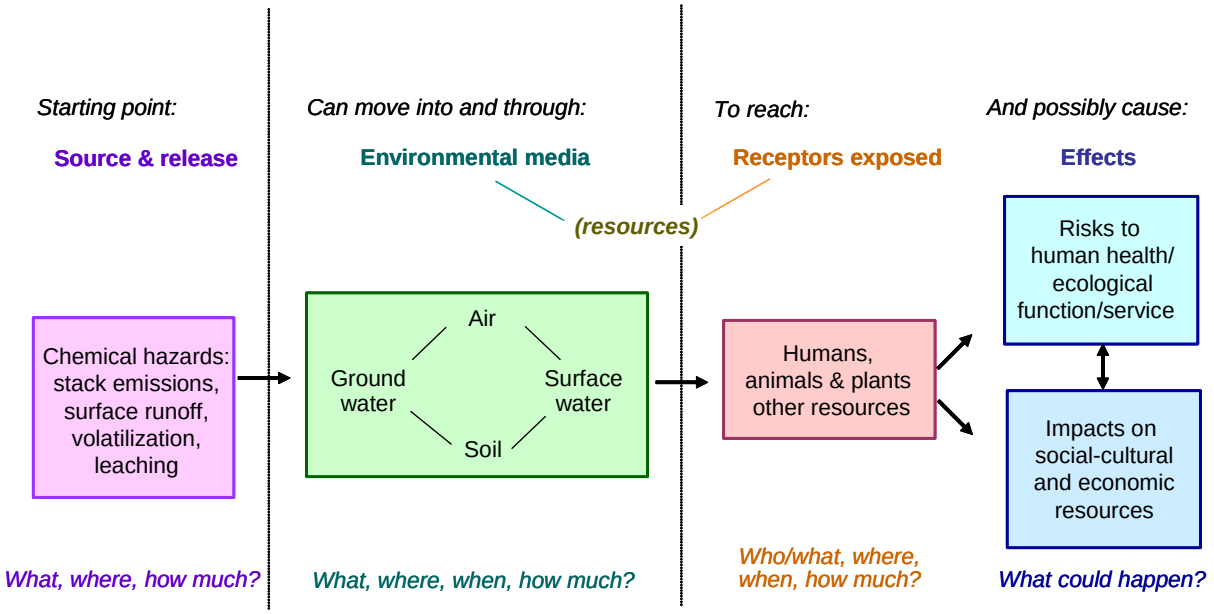


FIGURE 2-2

Key Elements of an Integrated Conceptual Model

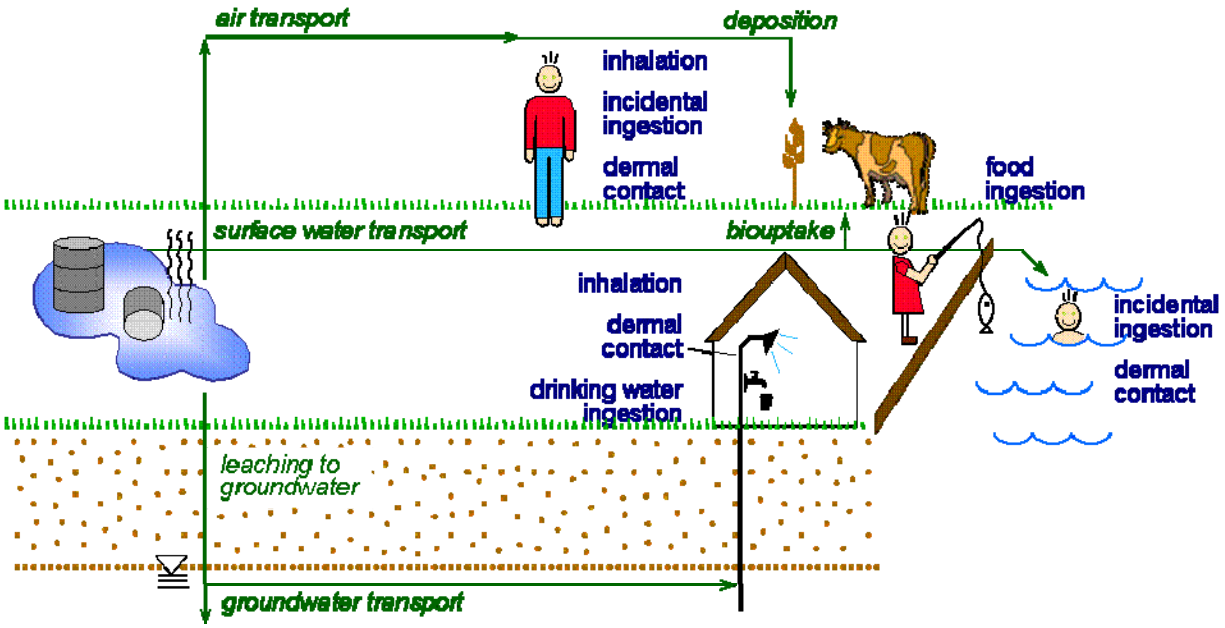


FIGURE 2-3

Schematic of Sources/Releases, Transport/Fate, and Exposure Routes

in Chapter 3 (e.g., Figures 3-5, 3-9, 3-11, 3-12) that suggest specific mechanisms and processes to be evaluated.

Conceptual models for cumulative risk cannot present all the complexities, especially those dealing with physical and toxicologic interactions. Consideration of all combinations and their potential interactions can be conceptually difficult and impractical, so that some kind of sorting or reduction of the potential combinations of chemicals, routes, effects must be first undertaken. That step is better represented by a decision tree or influence diagram. A site oriented, second-tier conceptual model may also be useful, as depicted in Figure 2-4. In addition to the usual boxes describing the scenario, processes, receptors, etc., there are also indications of places where environmental, toxicokinetic and toxicodynamic interactions could be considered. Those potential interactions can then be simplified by grouping (e.g., Section 3.3.2.2 for exposure based grouping) and prioritized using decision criteria. For example, toxicologic interactions could be screened based on toxicologic significance, as indicated by the relative importance of each chemical's environmental concentration using screening values such as the hazard quotient. Schematics and decision flowcharts for joint toxicity and toxicologic interactions are given in Figures 4-6a, b, and c. Once that initial screening or grouping is done, a revised conceptual model could be created, followed by more detailed analysis of the toxicologic interactions such as is described in Chapter 4.

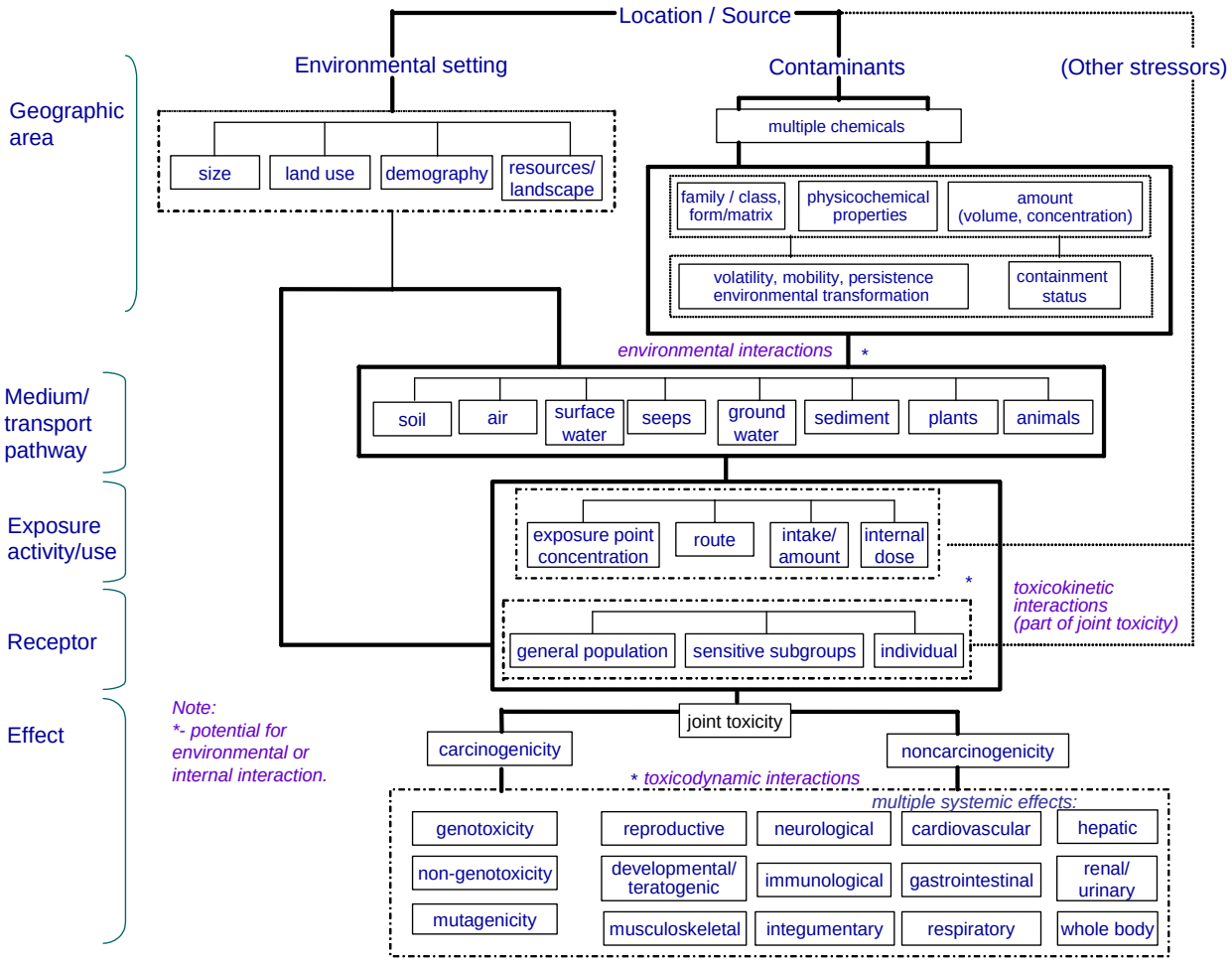


FIGURE 2-4

Example Second-tier Detail of the Conceptual Model for Cumulative Health Risk

3. CUMULATIVE EXPOSURE ASSESSMENT

This chapter provides detailed information on cumulative exposure assessment, to be conducted after completion of the steps described in Chapter 2, i.e., identifying the exposed population, conducting an initial exposure assessment, and developing a conceptual model for a cumulative assessment. The goal of Chapter 3 is to describe cumulative exposure assessment issues, highlighting existing data, methods and approaches that can be used to address these issues. To answer the questions for cumulative exposure assessments listed in Text Box 3-1, methods are described that can be used to determine if individuals are co-exposed to multiple pollutants and the time periods over which these exposures occur (i.e., toxicologically relevant time periods). In Section 3.1, cumulative exposure assessment is defined. In Section 3.2, an overview is provided of some documents that describe current Agency practice. Section 3.3 discusses the conduct of a population-focused cumulative exposure assessment, providing a brief overview of the basic steps undertaken in any exposure assessment and highlighting the issues that are not routinely evaluated in a conventional (i.e., single chemical-focused or single source-focused) exposure assessment. This includes grouping of potential chemicals of concern by exposure pathway and media with examples from different chemical groups (Section 3.3.2.2). In Section 3.4, cumulative concepts for atmospheric pollutants are illustrated. Finally, Section 3.5 summarizes the information in this chapter.

Cumulative Exposure Assessment Questions
(Text Box 3-1)

How can people be exposed to multiple chemicals?

In which media, at what levels, where and when?

What are the intensity and duration of these exposures?

Are there any unique subpopulation susceptibility or vulnerability issues?

3.1. DEFINING CUMULATIVE EXPOSURE ASSESSMENT

Exposure assessments that support cumulative health risk assessments evaluate a population's exposures to multiple chemicals through multiple routes of exposure over time. Such population-based assessments may need to consider multiple exposure timeframes: specifically, the timing and intensity of exposures to different chemicals may need to be evaluated relative to each other, based on an understanding of the potential toxicokinetic interactions and the potentially overlapping or complementary toxicodynamics associated with the chemicals of concern. In addition to evaluating exposures in the general population through standard environmental exposure pathways, exposure assessments that support cumulative health risk assessments also focus on the identification of potentially susceptible or vulnerable subpopulations in the study area and pathways of exposure unique to those subpopulations.

Cumulative exposure assessments rely on environmental occurrence data and environmental fate models to estimate the concentrations of multiple chemical pollutants in environmental media that individuals in the community may contact. Unlike chemical-focused assessments or single source-focused assessments, the community's boundary may define the geographic region of study. If the timing of different chemical exposures is important, then fate models may need to estimate changes in the concentrations in environmental media over time. The pollutants may occur in these media as a consequence of releases from multiple and different sources that could be located close to or distant from the population of concern. The environmental fate information needed for a community assessment could be site dependent; for example, the data could include the degradation of chemicals or chemical mixtures in the

environment, interactions of pollutants in the environment that influence their fate and interactions between chemicals and the environment (e.g., killing off or promoting soil microbes that normally degrade some of the chemicals or altering the soil binding so that transport through soils is enhanced).

3.2. EPA EXPOSURE ASSESSMENT GUIDANCE

The general methods the Agency uses to evaluate human exposures are presented in the *Guidelines for Exposure Assessment* (U.S. EPA, 1992a). Agency Program Offices follow these Guidelines and develop additional guidance documents that describe exposure assessment methods relevant to the specific types of chemicals they evaluate. For example, the basic process for assessing exposures at Superfund sites is described in the *Risk Assessment Guidance for Superfund* (U.S. EPA, 1989a) (see Text Box 3-2).

Selected Information Guides *(Text Box 3-2)*

Guidelines for Exposure Assessment (U.S. EPA, 1992a)

Risk Assessment Guidance for Superfund (U.S. EPA, 1989a)

Methodology for Assessing Health Risks Associated with Multiple Pathways of Exposure to Combustor Emissions (U.S. EPA, 1998a)

Human Health Risk Assessment Protocol for Hazardous Waste Combustion Facilities (U.S. EPA, 2005d)

DOE Information Brief: Baseline Risk Assessment Human Health Evaluation Manual (U.S. DOE, 1992)

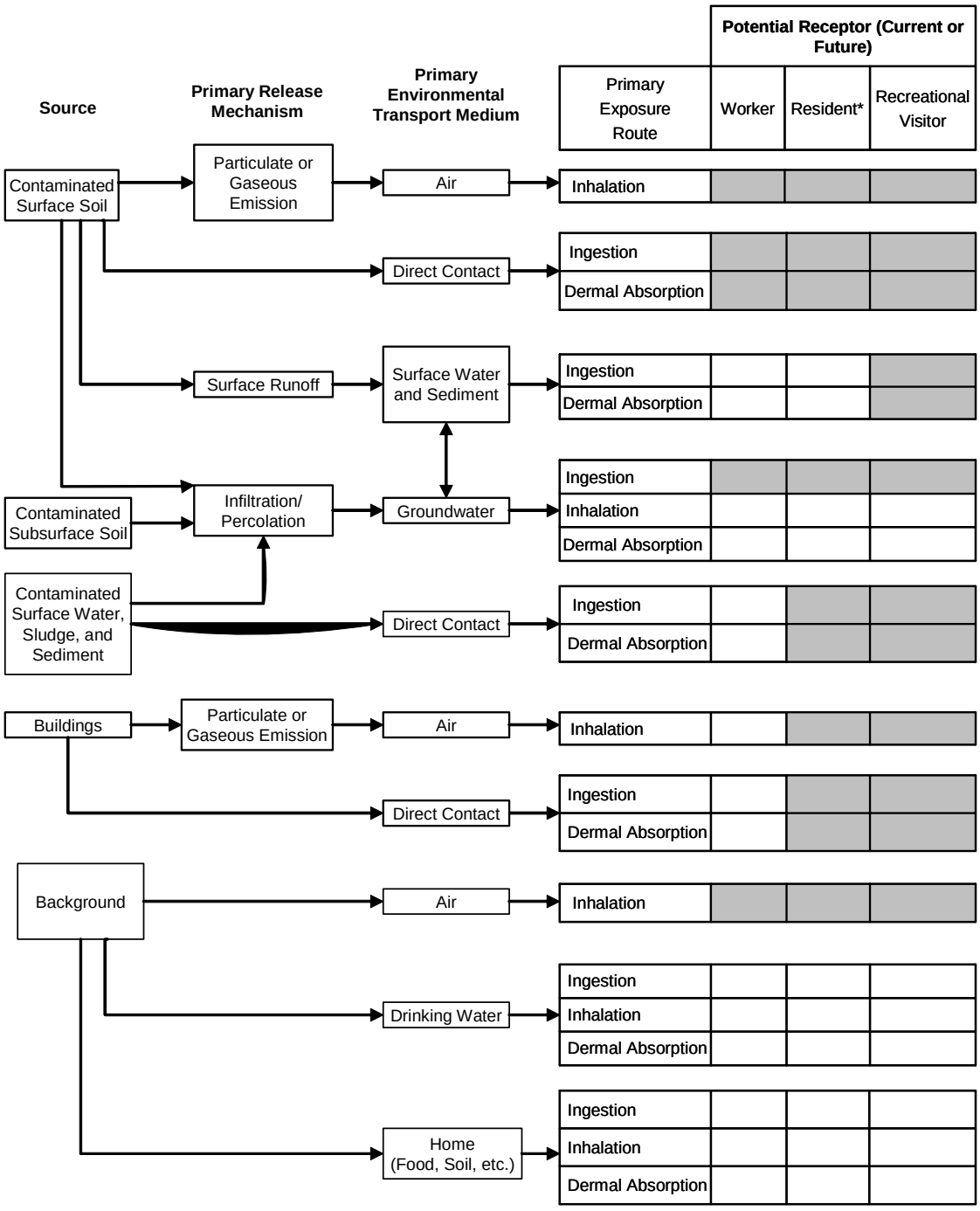
General Principles for Performing Aggregate Exposure and Risk Assessments (U.S. EPA, 2001a)

The assessment of exposures to chemicals released during combustion is described in *Methodology for Assessing Health Risks Associated with Multiple Pathways of Exposure to Combustor Emissions* (U.S. EPA, 1998a) and in *Human Health Risk Assessment Protocol for Hazardous Waste Combustion Facilities* (U.S. EPA, 2005d). While these documents focus on conventional exposure assessment approaches, many cumulative exposure assessment issues are presented.

At times, Program Office guidance is developed specifically to address cumulative exposure issues. For example, in response to the 1996 Food Quality Protection Act, the Office of Pesticide Programs developed *General Principles for Performing Aggregate Exposure and Risk Assessments* (U.S. EPA, 2001a). Finally, Agency documents that describe exposure approaches to chemical mixtures, such as the Site-Specific Assessment Procedures volume in the review draft *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo*-p-*Dioxin (TCDD) and Related Compounds* (U.S. EPA, 2003c), describe methods for examining chemical-specific cumulative exposure issues that can be applied in other situations. In summary, there are a number of Agency resources that describe methods and approaches that can be used to address various aspects of exposure assessments for community-based cumulative risk assessments.

3.3. CUMULATIVE EXPOSURE ASSESSMENT: ANALYSIS PHASE

As described in EPA risk assessment guidance documents, the analytic phase of an exposure assessment begins after a preliminary list of chemicals of potential concern has been developed and the population and subpopulations of concern have been identified. The materials presented in Chapter 2 identify data sources and approaches that can be considered when conducting a cumulative exposure. As described in Chapter 2, the linkages between relevant aspects of the analysis can be depicted using a conceptual model; Figure 3-1 provides an example conceptual model for a contaminated site. Although the initial triggers could vary across communities, as indicated in Figure 2-1, the same exposure assessment steps are addressed. The basic steps for quantifying human exposures to chemicals are identified in Text Box 3-3.



* The resident or visitor scenario may be expanded for cumulative assessments to consider unique exposures of specific sensitive populations (e.g., subsistence fishers).
Grey fill boxes indicate complete exposure pathways.
Open boxes indicate exposure pathways that are not complete.

FIGURE 3-1

Conceptual Model for Hypothetical Cumulative Exposure Assessments Illustrating Pathways Considered and Complete Pathways

In each section, cumulative exposure issues are identified and existing approaches are shown that can be used to address the issue. Typically, exposures are estimated for *complete* exposure pathways. Complete implies that each exposure assessment component is present from the occurrence of the chemical through relevant exposure pathways and routes to the receptor. Exposures may be estimated for pathways that are not currently complete but are considered likely to be complete be in the future.

Exposure Assessment: Analysis Steps
(Text Box 3-3)

Characterize the exposure setting (3.3.1)	Identify environmental features and potential receptors
Identify potential exposure pathways (3.3.2)	Describe sources, release mechanisms, receiving media, and locations for chemicals
Quantify exposures through multiple exposure routes (3.3.3)	Estimate medium-specific chemical concentrations at points of human exposure, and calculate intakes (considering time, frequency, duration)

3.3.1. Exposure Setting. Describing the environmental characteristics of the study area and identifying the people who are, or could be, exposed to multiple chemicals are the two main elements of the exposure setting for a community-based assessment. The following subsections describe cumulative assessment issues related to these elements.

3.3.1.1. Environmental Features — Characterizing the exposure setting potentially involves compiling basic data on topography, surface hydrology, soil geology, vegetation, groundwater hydrology, climate and meteorology, land use, pollution sources and demography of the community. Geographic and meteorological data are routinely assembled when conducting an exposure assessment. Basic geographic information about a community is available through sources offered by the U.S. Geological Service and U.S. Department of Agriculture; climate and meteorology data are generally available from the National Weather Service. Land use includes the

identification of all residential areas, work places, recreational areas and places where foods are grown or collected. Relevant pollution sources inside and outside[1] the community also need to be identified. Community input to these identification processes is important. This includes gaining an understanding of how different locations in a community are currently used and how they were used, which provides information on past polluting practices and potential past exposures.

In a community assessment, in addition to examining the contaminants present, there may be a need to examine environmental conditions in the broader region. For example, if there are atmospheric sources of concern for an affected community in which there is a Superfund site, a cumulative analysis may examine the concentrations in the local environment from these atmospheric sources and the potential for airborne contamination from the Superfund site as required by U.S. EPA (1989a). Ambient data that can be used in such an analysis can be obtained from various organizations, such as EPA regional offices and state, county, or city environmental agencies. (Several resources for these data are given in Appendix A.)

To illustrate how different types of data can be used, Text Box 3-4 illustrates data sources tapped for a recent cumulative study of air toxics in an urban area. The broader scope of a cumulative exposure assessment could include background data on chemical concentrations in local soil and water, both naturally occurring (such as metals) and anthropogenic chemicals (such as PAHs, PCBs, and dioxins) as well as concentrations of chemical pollutants in the U.S. food supply. For example, Volume 2, Properties, Environmental Levels, and Background Exposures, of the draft U.S. EPA

[1] For example, the analyst may wish to evaluate whether there are regional emissions sources that could be impacting pollutant levels in the community.

(2003c) dioxin document lists typical concentrations of dioxin congeners in the U.S. food supply. These nationally representative samples could be incorporated into a cumulative exposure analysis, if relevant. For example, such exposure pathways when combined with local exposure pathways could be shown to be a significant source of exposure.

Example Data Sources and Uses
(Text Box 3-4)

A recent air screening hazard assessment (U.S. EPA, 2004c) used data from several regional and local sources, including emissions data from the Toxics Release Inventory (TRI), Cumulative Exposure Project (CEP), and Regional Air Pollutant Inventory Development System (RAPIDS), as well as outdoor air monitoring data. These data were combined and compared to identify any consistently higher hazard areas, pollutants, and sources. Two methods were used to estimate relative inhalation hazards of outdoor air toxics: one for emissions mass (using TRI and RAPIDS data) and the other for outdoor concentrations (using CEP and monitored data). Emissions data enabled sources and release locations to be identified which improved the exposure assessment. (Note that TRI and RAPIDS emissions databases differ: TRI data are self-reported by facilities, while RAPIDS data are estimated by states from permits and other information sources.) Ambient data provided limited information on spatial distribution, without regard to specific sources. A weight-of-evidence approach was used to assess data among different sources.

The analysis of environmental features identifies potentially vulnerable populations (see Section 3.3.1.2) and the locations where people in a community could be exposed. Community members may provide valuable input into the locations of such sites, the relevant activities that may occur there, and the frequency with which a site is used. This information can provide insights into potential exposures and potential subpopulations being exposed through use of the location. Cumulative exposure assessments need to evaluate exposures where community members gather. For example, community members gather in schools and at playgrounds; an assessment may need to evaluate exposures in asthmatic children at these locations. Exposures that occur in and around facilities that care for the elderly and disabled members of a community may also require evaluation.

3.3.1.2. Receptor Characteristics Considered in Community-based

Cumulative Risk Assessments — In community-based cumulative risk assessments,

individuals and population groups that could be exposed to contaminants are identified during characterization of the exposure setting. Then, information on the residential locations, activity patterns, and workplaces is collected.

Cumulative assessments also examine exposures among both "typical" members of a community and vulnerable populations. Identification of the potentially vulnerable populations is typically developed jointly with dose-response analysts. U.S. EPA's *Framework for Cumulative Risk* (2003a) adopts "vulnerability" concepts described by Kasperson that encompass the topic of receptor characteristics. Four areas of vulnerability are articulated in the EPA document:

- differential exposure
- susceptibility/sensitivity
- differential preparedness and
- differential ability to recover.

Typical exposure assessments routinely identify some subpopulations that are, or may be, differentially exposed due to close proximity to a source or contaminated site and some exposure assessments also may identify subpopulations that exhibit activity patterns that may result in high exposures to pollutant concentrations. In these cases, detailed recreational uses and activity patterns are based on survey data, especially for fishing and hunting. Such data may be obtained from state or county departments of environment, conservation, natural resources, or parks and recreation. Community-specific surveys can be conducted to fill important gaps. If specific groups are, or could be, affected, they should be consulted to assess possible unique exposures. For

example, Native Americans may gather special vegetation or wildlife for food, medicine, or ceremonies or visit lands that are sacred.

Exposures in subpopulations exhibiting susceptibility/sensitivity, differential preparedness, and differential ability to recover are not always considered in typical exposure assessments but are given special consideration in a cumulative assessment. Exposures may be calculated separately for identified subpopulations with specific receptor characteristics to yield more realistic exposure estimates for those subpopulations. The receptor population characteristics considered in a cumulative assessment may include diverse factors such as genetic susceptibility, age, stress, disease state, economic status, ethnicity, health status, availability of health care, etc. It is particularly important to evaluate whether some potentially susceptible populations are exposed to high levels of pollutants. Examples of information resources that can be reviewed to support this evaluation are highlighted in Text Box 3-5. Pregnant women can represent a subgroup of special concern due to sensitivity for potential effects to the developing fetus. For example, the fetal nervous system is considered the most sensitive target of methylmercury and the U.S. EPA's reference dose (RfD) has been developed based on neurological effects associated with intrauterine exposures (U.S. EPA, 2001b).

Information for Susceptibility Assessment
(Text Box 3-5)

Type of Information	***Resources***
Demographic data	U.S. Census Bureau *(www.census.gov)*
Subpopulation groups	EPA report: *Sociodemographic Data Used for Identifying Potentially Highly Exposed Populations* (U.S. EPA, 1999c)
Locations (e.g., schools, hospitals, nursing homes)	Plat maps, city and county health departments
Exposure data (e.g., blood lead levels)	State registries, county and city health department reports
Cancer registries	Centers for Disease Control (national data and links to state cancer registries, *www.cdc.gov/cancer/npcr/statecon.htm*)
Other health effect registries	State registries of birth defects, asthma

Young children can be more biologically sensitive to many chemicals because certain protective body functions (e.g., liver enzyme production) are developing during the early stages of life. They also can incur higher exposures than the general population because of their different behaviors (e.g., pica or recreational swimming) and because their doses per unit body weight are higher than those of adults. Following the 1997 Executive Order for the protection of children from environmental health and safety risks, the Agency continues to develop approaches to account for differences such as body weights and toxicokinetics so risks to infants and children can be evaluated in further detail, whenever there appears to be a greater concern for adverse health effects than for the general population.

People with higher than average biological sensitivity to environmental stressors also include allergics and others with pre-existing medical conditions (e.g., asthma), especially when these individuals are housed together such as in hospitals or nursing homes. Some state health departments have established health registries for conditions such as asthma and for exposure measurements such as blood lead levels. These agencies can be consulted to determine if any clusters of affected individuals live in the community. Elderly and immunocompromised populations can be more susceptible to environmental exposures due to their health status. Other factors, like socioeconomic status, can affect access to health care or contribute to poor diet. Thus, poverty could indicate a potential increased susceptibility or biological sensitivity.

3.3.1.3. Cumulative Exposure Assessment Practices for Receptors — Once the land uses and sources of pollutants in the community have been identified (Section 3.3.1.1), it is common practice in exposure assessments to identify representative

default receptors, such as a current or future resident, trespasser, home gardener, and recreational angler. Exposures among these default receptors are subsequently estimated. The exposure factors associated with these receptors (e.g., quantities of homegrown vegetables consumed daily) can be obtained from sources such as the *Exposure Factors Handbook* (U.S. EPA, 1997c).

In typical assessments, the individual receptors are located in close proximity to a pollution source (e.g., at the fenceline, the nearest housing development, or the closest fishable lake). Cumulative assessments may evaluate other receptors who are, or could be, subjected to higher than average exposures, including people living near multiple sources of pollution (e.g., waste facilities, urban industrial areas, or transportation corridors) as well as residents of older homes with lead-based paint, and people whose jobs or recreational activities can cause specific chemical exposures or increased opportunities for exposure. Cumulative assessments also evaluate exposures in vulnerable populations (Section 3.3.1.2). If these screening practices do not reveal exposures of concern, then the receptors can be dropped from the analysis, after consultation with the dose-response analyst.

If the exposure levels are deemed to be of concern, then demographic data can be used to estimate the typical ages and ethnicity of these hypothetical community members who may be differentially exposed to pollutants from a source. These data may be used to refine the exposure estimate (see Section 3.3.3).

3.3.2. Exposure Pathways and Routes. An exposure pathway tracks how chemicals are transported from a source to an exposed person or subpopulation. An analysis of the exposure routes addresses how the contaminant can enter the body. The basic

process elements are summarized in Text Box 3-6. This section identifies considerations for how exposure pathways can be evaluated in an assessment.

The overall analysis plan for a risk assessment typically describes the general data, models, and assumptions that will be used to characterize exposure (Chapter 2). A main emphasis for cumulative assessments is on how sources, chemicals, media, and receptors can be grouped for joint pathway analyses. Various examples are offered in this section, with additional detail for one pathway (air) offered in Section 3.4 to illustrate how cumulative assessment issues can be considered.

Exposure Pathway Elements *(Text Box 3-6)*
Locations of sources, mechanisms by which chemicals could be released from sources, and identification of receiving environmental media
Transport of chemicals in the receiving media and movement from receiving media into other environmental media (e.g., from soil to air or water), degradation and transformation (change in speciation, sorption, etc.)
Estimated concentrations of contaminants at points of potential human contact (i.e., exposure points) and associated routes of exposure (e.g., incidental ingestion of soil, inhalation of airborne chemicals, or drinking water)

3.3.2.1. Sources and Fates of Chemicals and Chemical Mixtures —

Cumulative assessments of environmental contaminants identify all sources being considered and all potential exposure pathways for each medium of exposure. The pathways are then reviewed to determine if they are relevant to the study. The completeness of each exposure pathway is considered in determining whether it should be included in the evaluation. A pathway is complete when these four components are present:

- a source and a mechanism of contaminant release
- an environmental transport medium

- a point of human contact with the contaminated source or transport medium and
- a route of exposure at that point.

Criteria for inclusion are typically developed after discussion with the dose-response analyst so that resources can be efficiently focused on toxicologically relevant exposures. The pathways selected for inclusion are then characterized, and the exposures from all relevant pathways are jointly evaluated for the cumulative assessment.

In cumulative exposure assessments, an evaluation of environmental transformation of each chemical under consideration is a critical component for each selected pathway. While environmental transformation is recognized as a major factor for organic compounds, some metals can be altered in the environment, e.g., via methylation by biological processes, which can change bioavailability and toxicity.

Environmental transformation is a critical consideration when addressing exposures to environmental mixtures. For organic chemicals such as common solvents, environmental transformation or degradation can produce a number of new chemicals of potential concern in addition to those originally released. While some degradation products are less toxic than their parent compounds, this is not always the case. Thus, it is helpful to review historic operations records and other readily available data to consider additional contaminants that might warrant consideration. To illustrate, the solvent tetrachloroethylene is a common groundwater contaminant, and this volatile organic compound is converted over time to the more toxic vinyl chloride. Key properties of selected organic chemicals and degradation products are illustrated in Table 3-1 to show that data are available to characterize cumulative exposures.

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TABLE 3-1

Properties of Selected Organic Chemicals and Degradation Products to Demonstrate Availability of Such Information*

Chemical	Key Degradation Products	General Fate/Persistence	Environmental Half-Life	Log Kow (unitless)	Log Koc (unitless)	Indicative U.S. Concentration	IRIS Toxicity Value	Toxicity Relative to Parent
Pesticides								
Aldrin		Binds tightly to soil and does not leach readily, so is not usually found in groundwater; moderately persistent; bioaccumulates	Soil: 53-109 days (converts fairly rapidly to dieldrin)	6.50 (bioaccumu-lation likely)	7.67 (expected to strongly adhere to soil)	Air: 0.00003 ppb (mean); sediment: 1.3 ppb (mean) Gulf Coast	RfD: 0.00003	
	Dieldrin	As for aldrin, but very persistent;	Soil: 5 years	6.2 (bioaccumu-lation likely)	6.67 (expected to strongly adhere to soil)	Air: 0.0001 ppb (mean); soil: 1-49 ppb (mean); sediment: 3.2 ppb (mean) Gulf Coast)	RfD_i: 0.00005	60%
Chlordane	Not applicable, is not typically transformed in the environment	As for dieldrin, and in surface water will volatilize and adsorb to sediments	Air: 2.8 days (mean); water: 239 days; soil: 4.2 years (mean) (U.S. EPA, 2000b)	5.54 (bioaccumu-lation likely)	4.06 (mean) (expected to adhere to soil)	Surface and ground water: 0.1 ppb (mean) in specific areas; soil: <1 ppb -141 ppm	RfD: 0.0005	

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TABLE 3-1 cont.

Chemical	Key Degradation Products	General Fate/Persistence	Environmental Half-Life	Log Kow *(unitless)*	Log Koc *(unitless)*	Indicative U.S. Concentration	IRIS Toxicity Value	Toxicity Relative to Parent
DDT		Binds tightly to soil and does not leach readily, so is not usually found in groundwater; very persistent; bioaccumulates	Air: 37 hours; soil: 25 years (mean) but varies widely, depending on soil type and temperature	6.79 (bioaccumu-lation likely)	5.35 (expected to strongly adhere to soil)	Ambient water: 0.001 ppb (median); sediment: 0.1 ppb (median); soil: 4.67 ppb (geometric mean) mid-central United States	SF: 0.34 RfD: 0.0005	
	DDD	As for DDT	Air: 30 hours; soil: 10-15 years but varies widely, depending on soil type and temperature (CDC, 2003)	5.87 (bioaccumu-lation likely)	5.19 (expected to strongly adhere to soil)	Ambient water: >0.001 ppb (median); sediment: 0.2 ppb (median); soil: 1.20 ppb (geometric mean) mid-central United States	SF: 0.24	70%
	DDE	As for DDT	Air: 17 hours; soil: >20 years (mean) but varies widely, depending on soil type and temperature	6.00 (bioaccumu-lation likely)	5.19 (expected to strongly adhere to soil)	Ambient water: 0.001 ppb (median); sediment: 0.1 ppb (median); soil: 3.75 ppb (geometric mean) mid-central United States	SF: 0.34 RfD: 0.0005	Same as parent

2

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TABLE 3-1 cont.

Chemical	Key Degradation Products	General Fate/Persistence	Environmental Half-Life	Log Kow *(unitless)*	Log Koc *(unitless)*	Indicative U.S. Concentration	IRIS Toxicity Value	Toxicity Relative to Parent
Solvents								
Carbon tetrachloride		Stable in air; volatilizes rapidly into air from soil and surface water; very little binds to soil (most leaches into groundwater); stable in air; does not bioaccumulate	Air: 330 years; groundwater: 2.2 days (mean; with minerals); surface water: 9 months (mean for aerobic conditions), 17.5 days (mean for anaerobic conditions); soil: 6-12 months	2.64 (not likely to bio-accumulate)	2.04 (expected to move with ground-water)	Air: 0.168 ppb (mean); drinking water: 0.5 ppb (mean), for the 3% of samples with detectable levels	RfD: 0.0007	
	Chlorine (in air)	In air and water, reacts with water to form hypochlorous acid and hydrochloric acid; volatilizes from soil; persists in groundwater; does not bioaccumulate	Surface water: 3 hours (mean)	0.85 (not likely to bio-accumulate) (TCEQ, 2003)	Not identified (organic carbon in soil does not appear to play a major role)	Air: 807 ppb (mean)	RfD: 0.1	0.7%
	Chloroform (in water)	Persistent in groundwater; does not bioaccumulate	Surface water: 44 days	1.97 (not likely to bio-accumulate)	2.03 (mean) (expected to move with ground-water)	Drinking water: 23 ppb (mean)	RfD: 0.01	7%

TABLE 3-1 cont.

Chemical	Key Degradation Products	General Fate/Persistence	Environmental Half-Life	Log Kow *(unitless)*	Log Koc *(unitless)*	Indicative U.S. Concentration	IRIS Toxicity Value	Toxicity Relative to Parent
Tetrachloro-ethylene		Volatilizes rapidly from surface water and soil; leaches rapidly from soil to groundwater; does not bioaccumulate	Air: 134 days (mean); groundwater: estimates vary from 9 months to 1 billion years (hydrolyzes), differences likely due to errors in extrapolation and presence/absence of microbes; surface water: volatilization half-life is <4 hours; soil: volatilization half-life is 2 to 16 days	3.40 (not likely to bio-accumulate)	2.5 (mean) (expected to moderately bind to soil and moderately move with ground-water)	Air: 0.50 ppb (mean) including areas close to emission sources; drinking water: 0.75 ppb (median) from ground water, for the 8% of samples with detectable levels; sediment: 5 ppb (median)	RfD: 0.01	
	1,1-Dichloroethylene	Volatilizes relatively quickly from surface water and soil; moves with groundwater; stable in water; does not bioaccumulate	Air: 2.5 days (mean); surface water: 4 days (mean), volatilizes	1.3 (not likely to bio-accumulate)	1.81 (not expected to bind to soil; expected to move with ground-water)	Air: 4.6 ppb (mean); drinking water: 0.6 ppb (mean) for the 3% of samples with detectable levels	RfD: 0.05	20%

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TABLE 3-1 cont.

Chemical	Key Degradation Products	General Fate/Persistence	Environmental Half-Life	Log Kow *(unitless)*	Log Koc *(unitless)*	Indicative U.S. Concentration	IRIS Toxicity Value	Toxicity Relative to Parent
	trans-1,2-Dichloroethylene (cis- degradation products also form; trans- is shown here because an RfD exists for this compound)	Volatilizes quickly from surface water and soil; moves with groundwater; does not bioaccumulate	Air: 8.5 days (mean); groundwater: 30.5 weeks (mean); surface water: 4.6 hours (mean) (volatilizes)	2.09 (not likely to bio-accumulate)	1.56 (not expected to bind to soil; expected to move with ground-water)	Air: 0.037 ppb (median); drinking water/ groundwater: 173 ppb (mean)	RfD: 0.02	50%
	Trichloro-ethylene	Volatilizes quickly from surface water; binds to soil; persistent in groundwater; does not bioaccumulate	Air: 7 days; groundwater: estimates vary widely from 10 months to 1 million years (hydrolyzes), differences likely due to errors in extrapolation and presence/absence of microbes); mean volatilization half-life in surface water is 2 hours from modeled data, and 20 days from measured data;	2.42 (not likely to bio-accumulate)	2.35 (mean) (expected to moderately bind to soil and moderately move with ground-water)	Air: 0.56 ppb (mean) including areas close to emission sources; drinking water: 1 ppb (median) from groundwater, for the 10% of samples with detectable levels; sediment: <5 ppb (median)	N/A	

2

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TABLE 3-1 cont.

Chemical	Key Degradation Products	General Fate/Persistence	Environmental Half-Life	Log Kow *(unitless)*	Log Koc *(unitless)*	Indicative U.S. Concentration	IRIS Toxicity Value	Toxicity Relative to Parent
	Vinyl chloride	Volatilizes quickly from surface water and soil; moves with groundwater; does not bioaccumulate	Mean volatilization half-life is 29 hours in surface water and 12 hours in soil	1.36 (not likely to bio-accumulate)	1.99 not expected to bind to soil; expected to move with ground-water)	Air: 5 ppb (mean) neighborhood close to hazardous waste site; drinking water: detected in 0.74% of groundwater supplies, maximum concentrations of 1.1 and 8.4 ppb, for random and nonrandom sites, respectively	RfD: 0.003	333%
Trichloro-ethylene		As for tetrachloroethylene					N/A	
	1,1-Dichloroethylene	As for tetrachloroethylene					RfD: 0.05	0.6%
	trans-1,2-Dichloroethylene (cis- also forms)	As for tetrachloroethylene					RfD: 0.02	1.5%
	Vinyl chloride (in water)	As for tetrachloroethylene					RfD: 0.003	10%

2

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TABLE 3-1 cont.

Chemical	Key Degradation Products	General Fate/Persistence	Environmental Half-Life	Log Kow *(unitless)*	Log Koc *(unitless)*	Indicative U.S. Concentration	IRIS Toxicity Value	Toxicity Relative to Parent
Nitroaromatic Compounds								
2,4,6-Trinitrotoluene		Can leach relatively quickly from soils to groundwater; can bioaccumulate but not to a large extent	Air: 7.5 hours (mean); surface water: 43 minutes (mean), catalyzed by sunlight; groundwater: 6 months or longer (mean), varies; soil: 3.5 months (mean)	2.2 (mean) (not likely to bio-accumulate)	2.76 (mean) (tends to moderately bind to soil and moderately move with ground-water	Groundwater: 1-320 ppb in contaminated areas; soil: 24,000 ppm (mean) in highly contaminated areas	RfD: 0.0005	
	Nitrobenzene	Leaches to groundwater; does not bioaccumulate	Soil: 7 days (aerobic biodegradation) or 22 days (anaerobic degradation); surface water: 40 days	1.87 (not likely to bio-accumulate)	1.56 (not expected to bind to soil; expected to move with ground-water)	Air: 0.12 ppb (mean)	RfD: 0.0005	Same as parent

2
3

TABLE 3-1 cont.

* Organic compounds illustrated here are often found at Superfund sites; others also commonly found include acetone, benzene, 2-butanone, chloroform (included above as a degradation product), 1,1-dichloroethene, methylene chloride, naphthalene (designated by EPA as "pending" for this list), pentachlorophenol, polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs) (designated by EPA as "pending" for this list), toluene, vinyl chloride, and xylene (designated by EPA as "pending" for this list). (Source: EPA's *Common Chemicals Found at Superfund Sites*, see http://www.epa.gov/superfund/resources/chemicals.htm.) Trinitrotoluene is also included here because of its presence at certain federal sites. Much of the fate information and environmental levels are from the ATSDR toxicological profiles (see below). Toxicity values are oral reference doses (RfDs) as mg/kg-day and oral slope factors (SFs) as per mg/kg-day from the Integrated Risk Information System (IRIS) current through November 2005 (U.S. EPA, 2005c). N/A = not available. Gray shading indicates the entry is not applicable because this is the parent compound.

Environmental half-life is used to generally represent the time it takes for the initial amount of a chemical to be reduced by half in the indicated medium. The Kow indicates whether a chemical is hydrophilic and will be predominantly found in water, or is lipophilic and will be found in fatty tissue of animals or associated with other organic materials in aquatic systems. The Kow values are presented as logarithms because this measure varies widely across compounds. A log Kow of 0 indicates an equal affinity for lipids and water. A high log Kow indicates the chemical is not very soluble and will not move with water; a low log Kow indicates the chemical is very soluble and will move with water (it also indicates the chemical will be readily absorbed from the gastrointestinal tract after being ingested or from the lungs after being inhaled). As the log Kow increases, the solubility in lipids increases, which means the potential to bioconcentrate in aquatic organisms increases; when the log Kow reaches 5 to 6 it indicates the chemical can bioconcentrate significantly in aquatic organisms, but as it increases above 6, the chemical is less likely to bioconcentrate, approaching no bioconcentration at a log Kow of 12. (Source: EPA *Pollution Prevention (P2) Framework, Physical and Chemical Properties Models*, see http://www.epa.gov/oppt/p2framework/docs/pchem.htm.)

The Koc indicates how the organic compound will partition between water and the organic carbon portion of soil/sediment and biota. The Koc indicates whether or not a chemical will move with ground water. These are also presented as logarithms because this measure also varies widely across compounds. A high log Koc (e.g., 3.5 or higher) indicates the chemical is likely to sorb to soils, sediments, or sludges and is less likely to move with surface water or groundwater. A low log Koc (e.g., 2.4 or below) indicates the chemical is not likely to sorb to soils, sediments, or sludges, and thus is more is likely to move with water. Contaminants with a log Koc between 2.4 and 3.5 likely partition to soils, sediments, or sludges and surface water or groundwater. (Source: EPA *Pollution Prevention (P2) Framework, Environmental Fate Models*, see http://www.epa.gov/oppt/p2framework/docs/envfate.htm).

(Sources: ATSDR, 1990, 1994a,b, 1995, 1996, 1997a,b,c,d, 2002a,b; CDC, 2003; U.S. EPA, 1999b,d, 2000b, 2001c, 2003d, 2005d,e; IPCS, 1982)

When evaluating environmental fate and transport across media for these assessments, it is important, but not mandatory[2], that mass should be maintained when predicting concentrations of parent chemicals and degradation products. Chemical speciation can also be important for cumulative risk assessments. Different oxidized or reduced forms of metals react differently in the environment and have different toxicities; trivalent and hexavalent chromium provide a good example, with the latter being much more toxic. Thus, it is important to characterize the soil and water chemistry at sites to assure that appropriate physicochemical characteristics are being reflected in the assessment. In evaluating combined chemicals, care must be taken to assure that assumptions are internally consistent among all chemicals within a given setting. For example, assuming the presence of a reduced form of a metal may be incorrect, especially in an aerated environment where other chemicals are assumed to be in the oxidized form.

For radioactive compounds, the natural physical decay process causes radionuclides to change over time. For these contaminants, natural attenuation (radioactive decay) will reduce contaminant levels over time. The basic concepts of half-life and natural attenuation over time are illustrated in Figure 3-2 (from Brown, 1999, as cited in U.S. DOE, 1999). Table 3-1 shows that the half-life for tritium is approximately 123 years. Figure 3-2 illustrates natural attenuation over time showing that ambient levels of tritium are predicted to be approximately 10% of original levels after 50 years. The parallel evaluation for nonradioactive chemicals reflects environmental half-life.

[2] Some useful models do not maintain mass balance.

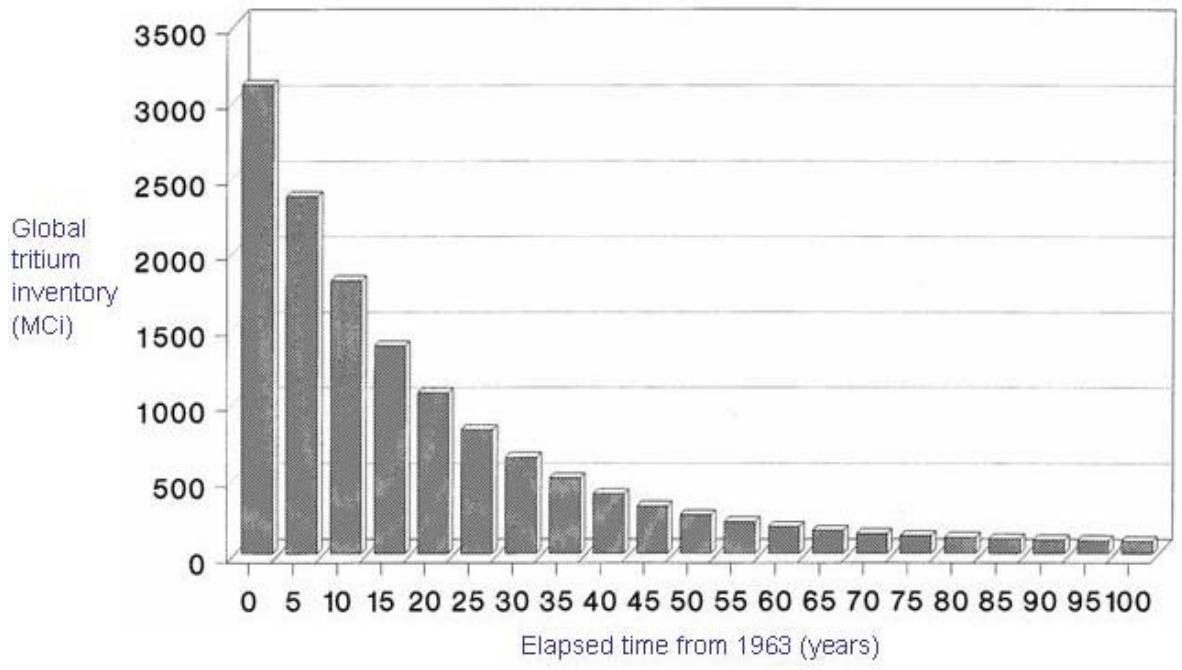

FIGURE 3-2

Illustration of Global Background from Atmospheric Fallout of Tritium
Source: Brown (1999)

Once released from different sources in various forms, chemicals can migrate to other locations and media. The degree to which a particular chemical substance favors a given transport path depends on the form of the chemical released, its physical state, and the nature of any particulate matter to which it might adsorb upon or following release. These pathways are generally predictable from the known release processes and expected physical forms of the chemicals.

The transport and fate of mixtures of chemicals released to the environment are not random but can be predicted to varying degrees by considering a number of factors related to the release, migration, and persistence of their constituents. Following release from a source, mixture components are typically differentially transported through the environment. These chemical mixtures are subject to transformation reactions in the environment which can change their composition. Some chemicals are degraded, while others are formed through various environmental reactions. Changes in the mixture composition can be specific to the environmental medium. It is important to document these changes in the mixture composition. (The differential nature of transport can be an important consideration in the toxicity of a mixture because the composition of the mixture to which a community is exposed could be very different from the mixture that has undergone toxicological testing. See discussion of sufficient similarity in U.S. EPA, 2000a.[3]) It is useful to consider three types of transfers that can occur between environmental compartments:

[3] *Sufficient similarity* is a key concept for evaluation of a complex mixture. It is applied when inadequate toxicity data are available directly on a mixture of concern, but toxicity data can be acquired on a mixture composed of similar chemical components in similar proportions. If the two mixtures are judged to be sufficiently similar, then the toxicity data for the latter can be used as surrogate data in conducting a quantitative risk assessment for the mixture of concern. The U.S. EPA has proposed this general concept for the evaluation of complex mixtures in its risk assessment documentation (U.S. EPA, 2000a). The exposure analyst and dose-response analyst should jointly discuss this issue.

- differential transfer between different abiotic media (e.g., soil and surface water)
- differential transfer between abiotic and biotic media and
- differential transfer between different biotic media.

Mixture components can be differentially transferred between abiotic media. For example, drinking water disinfection by-products (DBPs) such as chloroform and bromodichloromethane are highly volatile; others, such as monochloroacetic acid, are not (U.S. EPA, 2003b). Consequently, the composition of a DBP mixture in the indoor air differs considerably from the DBP mixture in a glass of water. The insecticide toxaphene provides a second example. Technical grade toxaphene, which contains over 670 chemicals, was one of the most heavily used insecticides in the United States until 1982 when it was canceled for most uses. It was used primarily in the southern United States to control insect pests on cotton and other crops. Some components of technical toxaphene may volatilize to air; others do not dissolve well in water. The composition of the toxaphene mixture will differ depending on whether it is measured in soil at a hazardous waste site, the air around the site, or sediment at the bottom of lakes or streams near the site (ATSDR, 1996).

Mixture components can be differentially transferred between abiotic and biotic media. For example, the Site-Specific Assessment Procedures volume in the review draft *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo*-p-*Dioxin (TCDD) and Related Compounds* (U.S. EPA, 2003c) provides methods for predicting differential uptake of different dioxin congeners from the atmosphere into plant tissue and the selective retention of dioxin congeners in fish adipose tissues.

Some components of technical toxaphene have been measured in shellfish and fish (ATSDR, 1996).

Mixture components can be differentially transferred between biotic media. For example, the Site-Specific Assessment Procedures volume in the review draft *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) and Related Compounds* (U.S. EPA, 2003c) provides methods for predicting the selective uptake and retention of different dioxin congeners from grass into the adipose tissues of grazing cattle.

3.3.2.2. Grouping Chemicals for Cumulative Risk Analysis — Mixtures occurring in a community may originate from different sources. In this section, a set of six tables is provided that illustrates how information about sources of chemical pollutants, chemical properties, and fate can be organized to guide chemical groupings for cumulative risk assessments in contaminated communities. These tables provide context regarding the normal uses of chemicals often found in mixtures and their behavior in the environment that leads to their coexistence in media to which people can be exposed. The grouping of the chemicals should be based on the potential for their co-occurrence in each compartment/medium, potential for interactions affecting transformation, and potential for co-occurrence and interaction along each transport pathway between media. Figure 3-3 provides an overview of how this information might be organized according to media and the processes of fate and transport.

While chemicals can be easily grouped based on common sources and releases (e.g., chemicals in diesel exhaust), the usefulness of groupings for various chemical classes can be improved based on typical primary release mechanisms that would be

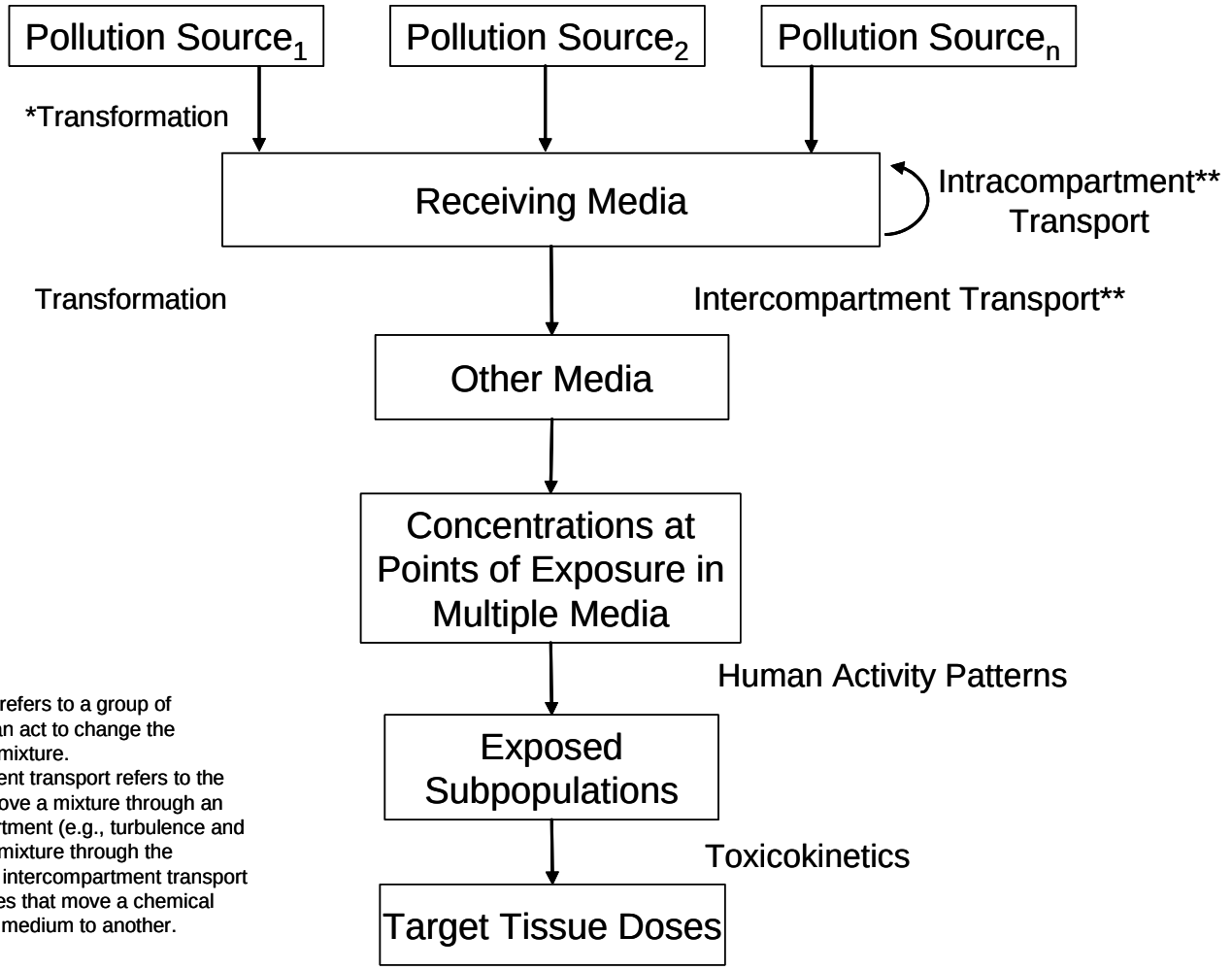

FIGURE 3-3

Approach for Estimating Exposure in Cumulative Risk Assessments

expected to control initial contamination and migration behavior in the environment, as illustrated in Table 3-2. Released chemicals can disperse quickly over a fairly wide area by convection (such as via wind or surface water flow), and they can also migrate following waste placement. The dominant processes at a given location determine what will be the "receiving medium" into which a particular class of chemicals is introduced and from which they can migrate.

Contaminant properties relevant to fate and transport include volatility, water solubility, and partition coefficients for:

- water and available organic phases (as represented by the octanol-water partition coefficient, Kow)
- water and solid phases (Kd) and
- water and air (Henry's constant, K_H).

Additional properties for soil and sediment include the fraction of organic carbon (foc) and the clay content, which indicates the amounts and types of sorption sites available. Table 3-3 can be used to group chemicals per their expected general partitioning in media based on well-known physical constants for the chemicals and media. Chemical-specific soil-water partition coefficients in various soil textures can be displayed to help evaluate possible chemical grouping based on similar mobility, as shown in Figure 3-4.[4] The soil type, geochemistry, and other data should be evaluated in determining generally appropriate values, and site-specific studies are important to the selection of the actual values for key contaminants.

To illustrate how grouping tables can be applied to assess multiple chemicals in different classes for a cumulative risk assessment, an example is offered for PCBs

[4] Note that the Kd values overlap given the wide range of soils used to develop the figure. Kd values for specific types of soil or additional data may be needed to implement this grouping step.

TABLE 3-2

Grouping Chemicals by Common Migration Behavior

Migration Initiation Process	Organic Chemicals	Inorganic Chemicals and Gases
Volatilization to air	Chlorinated solvents Petroleum-based solvents Fuels	Cl_2, ammonia, tritium, SO_2, NO_x, CO, CO_2
Dissolution in groundwater	Chlorinated solvents Aromatic hydrocarbons (BTEX) Pesticides	Cations Anions
Dissolution in surface water	Phenols, amines, ethers, alcohols, organic acids	Cations and anions (e.g., perchlorates)
Particulate emissions from combustion (stacks)	Products of incomplete combustion (PICs) - PCBs, PAH, dioxins, furans	Heavy metals
Gaseous emissions from combustion (stacks)	Light hydrocarbons	SO_2, NO_x, CO, ammonia
Dust-blown migration	Nonvolatile organics - PAHs, PCBs, dioxins	Heavy metals
Waste placement	All listed above	All listed above
Leaching to groundwater	Chlorinated solvents (DNAPLs)	NA

Heavy metals are as indicated in Table 3-1. Acronyms not previously defined (in Table 3-1) are: CO=carbon monoxide; CO_2=carbon dioxide; DNAPLs=dense non-aqueous phase liquids; and SO_2=sulfur dioxide.

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TABLE 3-3

Grouping Chemicals by Environmental Fate Measures[a]

Environmental Compartment	Persistence (environmental half life)	Environmental Partitioning (equilibrium-based)[b]	Mobility (convection- and dispersion-based)
Organic matter in soil and sediments, soil organisms	High for: High Kow/Kd Low biodegradability Low for: High Kow/Kd High biodegradability	Presence favored by: High Kow/Kd High persistence	High binding for: High-Kow/Kd organics and inorganics Low binding for: Low-Kow/Kd organics and inorganics
Soil inorganic phase	High for: High-Kd inorganics, Low-Ksp inorganics (including metals that form complexes in soil) Low for: Low Kow/Kd organics/inorganics	Presence favored by: High-Kd and low-Ksp inorganics	High mobility for: Cations, anions, water- soluble organics (low Kow/Kd) High-Ksp colloids Low mobility for: High-Kow/Kd organics High-Ksp solids

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TABLE 3-3 cont.

Environmental Compartment	Persistence (environmental half life)	Environmental Partitioning (equilibrium-based)[b]	Mobility (convection- and dispersion-based)
Surface water	Higher for: Insoluble (high Kow) Non-photodegradable Non-biodegradable Lower for: Water soluble (low Kow) Volatile (low K_H) Photodegradable Biodegradable	Presence favored by: Low Kow/Kd High K_H (low volatility to air) High-Ksp inorganics	High transport for: High solubility Low volatility Low transport for: Precipitates (low Ksp) Low solubility (high Kow) Biodegradable Photodegradable
Groundwater	Higher for: Low biodegradable DNAPL-forming Lower for: Biodegradable Highly soluble (low Kow/Kd) LNAPL-forming	Presence favored by: High solubility (low Kow/Kd) Ionic forms (cations and anions) High-Ksp inorganics	High mobility for: Low Kow/Kd organics and inorganics Ionic forms Low mobility for: High Kow/Kd organics and inorganics Inorganic solids

TABLE 3-3 cont.

Environmental Compartment	Persistence (environmental half life)	Environmental Partitioning (equilibrium-based)[b]	Mobility (convection- and dispersion-based)
Air	Higher for: Low photodegradable Low reaction rate with hydroxyl radical & other free radicals Low wash out rate (low K_H) Gas phase Lower for: Photodegradable High reaction rates High wash out (high K_H) Particulate phase	Presence favored by: High volatility substances (gases and low boiling point liquids) High volatility from water (low K_H)	High mobility for: Gas phase High persistence Small-particle bound Low mobility for: Low persistence Large-particle bound
Aquatic and terrestrial biota	Higher for: Lipid soluble (high Kow) Non-biodegradable Low depuration rates Lower for: Water soluble (low Kow) High depuration rates due to: enzyme-oxidizable and/or forms complexes with GHS, other agents	Presence favored by: High organic solubility (high Kow) High BCF Persistence in biota/prey (high BAF)	Mobility enhanced by: High persistence in biota High vegetative uptake factors (high Kow), specific binding factors) Mobility reduced by: High degradation rates High elimination rates Low uptake factors

[a] Acronyms not previously defined: BAF=bioaccumulation factor, BCF=bioconcentration factor, GHS=glutathione, LNAPL=light non-aqueous phase liquid, Kd=soil/water partition coefficient, K_H=Henry's constant (water/air distribution constant), Kow=octanol/water partition coefficient (octanol approximates soil organic matter, or biomass), Ksp=solubility product constant for inorganic complexes.

[b] "Presence favored by" indicates that concentrations would be relatively higher compared to adjacent compartments, i.e., activity coefficients for the substances are relatively low in the given compartment/medium.

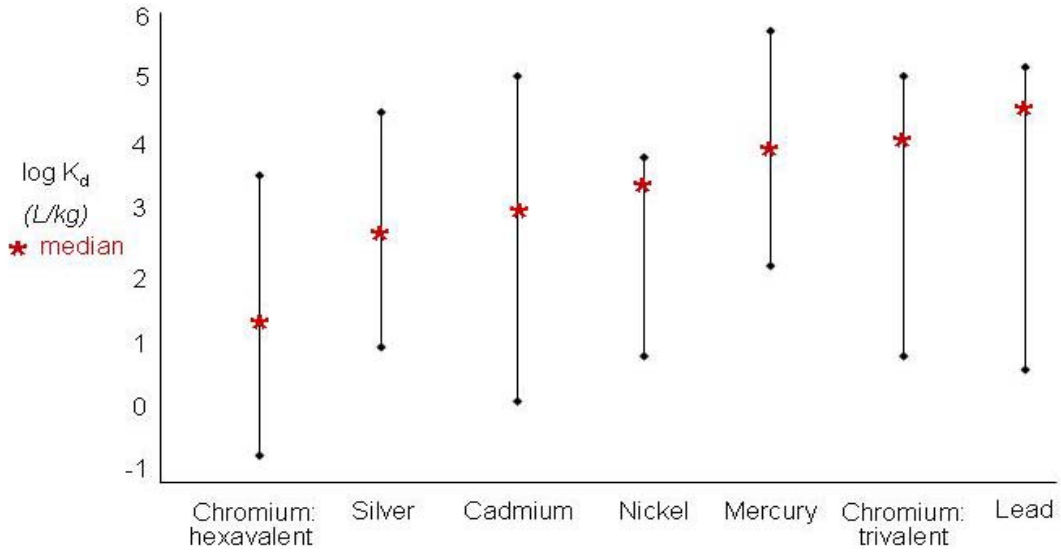

FIGURE 3-4

Assessing Relative Mobility in Soil to Support Chemical Groupings
(Source: represents soil-water partition coefficient data from U.S. EPA, 1999d)

(representing a group of congeners). First, the properties for PCBs are discussed, and then other chemicals and chemical classes that might be included in the PCB groups based on their similar physical-chemical properties are identified. The general grouping information in Table 3-3 can be combined with illustrative parameter information in Tables 3-4 and 3-5, and from this information, the persistence of PCBs in soil organic matter would be expected to be high given the high Kow values and low biodegradability. Also, concentrations would likely be high in soil organic matter compared to other media such as soil inorganic matter or soil pore water, again because high Kow values indicate higher partitioning to organic phases. Their mobility in soil would be controlled by two processes: dissolution in water (e.g., moving laterally as surface transport or generally downward with percolating water) and retardation due to sorption onto inorganic soil particles (assuming foc is low for subsurface soils, as the near-surface soil horizons contain the bulk of organic matter that has not yet been mineralized).

In this example, groundwater concentrations of PCBs are expected to be very low based on likely partitioning of PCBs to solids in the soil. If some PCB congeners could migrate through the soil and reach the groundwater, this would lead to dilute PCB congener concentrations in this medium. The concentrations reaching groundwater would likely be very low, perhaps undetectable by usual measurement methods. In addition, the congener composition would change during transport, in accordance with the varying solubility and sorption properties of compounds with different levels of chlorination (e.g., more highly chlorinated compounds are less soluble). Additional data show that PCBs degrade slowly in soils.

TABLE 3-4

General Grouping Categories for Key Fate Parameters[a]

Parameter[b]	General Categories and Examples		
	Low	Medium	High
Partition coefficient: Kow	<100	100 to 10,000	>10,000
Solubility product: Ksp	$<1 \times 10^{-50}$	1×10^{-10} to 1×10^{-50}	$>1 \times 10^{-10}$
Water solubility: Sw *(ppm)*	<10	10 to 1000	>1000
Henry's constant: K_H *(mol/L*atm)*	<0.01 to 1	1 to 1000	>1000
Vapor pressure: VP *(mm Hg)*	<0.001	0.001 to 1	>1
Melting point : MP (*^oC)*	<0	0 to 100	>100
Boiling point: BP *(^oC)*	<50	50 to 300	>300

[a] General ranges indicated in this table illustrate the principles outlined in Table 3-3; other general bounds would also be appropriate. For example, a Ksp of 10^{-5} could be used as a delineator for "readily soluble" for one-molar electrolyte solutions, while formal water solubilities <0.003 mole/liter could indicate the compound is "not readily soluble."

[b] Kow is the partition constant between water and octanol, which represents a generic "organic" phase; this coefficient applies mainly to organic chemicals (those containing carbon). Ksp is the solubility product of inorganic compounds, which describes the equilibrium between the (excess) solid form and dissolved (or solvated) ions, and is used to determine if a solid is readily soluble in water. The Ksp is a function of the water solubility, Sw. K_H is the distribution constant for a chemical between air and water phases, based on the partial pressure of the gas above the solution to its dissolved concentration; the extent to which a given gas dissolves in solution (here, water) is proportional to its pressure (Henry's law), and K_H is the proportionality constant for this relationship. VP is the pressure exerted by a vapor in equilibrium with its solid or liquid phase, typically used for a vapor in contact with its liquid (so it would represent the vapor-phase pressure of the pure liquid). MP and BP, the melting and boiling point s, are simple physical constants; they are used here to help guide the grouping of organic chemicals.

TABLE 3-5

Specific Parameter Values for Example Chemicals[a]

Chemical[b]	Kow (unitless)	K_H (mol/L*atm)	Ksp (unitless)	Sw (ppm)	BP (^oC)	VP (mm Hg)	MP (^oC)
Toluene	540	0.15	NA	526	111	28	-95
Trichloroethylene	260	0.1	NA	1,280	87.2	69	-84.7
Phenol	29	3,000	NA	83,000	182	0.35	40.9
Benzo(a)pyrene	1,300,000	2,200	NA	0.001	311	5×10^{-9}	176.5
PCBs	12,600,000	2.4	NA	0.7	NA	0.0005	NA
Dioxin (2,3,7,8-TCDD)	6,300,000	20	NA	0.0002	NA	1.5×10^{-9}	305
Pentachlorophenol	132,000	40,800	NA	14	309	0.0001	174
Atrazine	410	420,000	NA	35	NA	3×10^{-7}	173
Mercury (Hg)	4.2	0.12	NA	0.06	357	0.002	-39
Hg sulfide (HgS)	NA	NA	1.6×10^{-52}	2×10^{-21}	NA	NA	NA
Lead chloride ($PbCl_2$)	NA	NA	1.6×10^{-5}	3,300	NA	NA	NA

[a] Parameters are defined in Table 3-4. NA=not applicable. Representative values shown here are taken from a number of sources and are offered simply for illustration; to calculate environmental behavior for a specific case, setting-specific information should be used to determine the appropriate value for a given parameter.

[b] Chemicals were selected to represent a wide range of physical properties, applications, and sources. Values for dioxin are for the tetrachlorodibenzodioxin isomer generally regarded as most toxic.

Moving down Table 3-3, one would predict that while PCB concentrations would be low to intermediate in soil inorganic phases and very low in surface water and groundwater, some volatilization to air might occur for low-chlorinated congeners as indicated by their relatively low boiling points and appreciable vapor pressures. Some volatilization from water would be expected based on the relatively low K_H values of PCBs. Migration through air might be possible via adsorption to particulate matter, and rain washout would depend on the relative fraction of PCBs in the vapor phase versus the particulate phase, as well as the partitioning between air and rain water as indicated by Henry's constant. (This constant defines the wet removal process for soluble gases; the effective Henry's constant is used to predict dry deposition velocity for gases and particles, in a calculation that also includes molecular weight and surface reactivity and diffusivity ratios.)

Further, expected levels of PCBs in aquatic and terrestrial biota (i.e., via food web transfers) might be high relative to surrounding media (water or inorganic soil), and these levels would be expected to persist due to high lipid solubility (high Kow) and low biodegradability. Finally, given their persistence in fatty tissues, these levels might be expected to be accumulated in the food chain; apex predators would likely have the highest concentrations.

Grouping of PCBs with other chemicals can then be explored by applying concepts presented in Table 3-3 using Tables 3-4, 3-5, and 3-6. As seen from Table 3-6, PCBs in soil organic matter could be grouped with other persistent organics such as PAHs (see Table 3-5 for details on benzo(a)pyrene), dioxins and atrazine.

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TABLE 3-6

Summary Comparison and Screening Suggestions

Media/Compartments	Suggested Chemical Grouping *(for contaminated sites, over time)*
Soil organic phase (upper soil horizon)	Low volatility, high Kow, persistent organics: *PCBs, dioxins, PAHs;* moderately persistent: *atrazine*
Soil inorganic phase (lower horizons)	High Kd inorganics: *Metal oxides, hydroxides, carbonates*
Aquatic sediments	High Kow organics, low Ksp inorganics: *PCBs, chlorinated pesticides, dioxins, insoluble metal complexes*
Surface water	High water-soluble organics, high Ksp inorganics: *Phenols, ethers, esters, nitro- and amino-organics, soluble metal complexes*
Groundwater	Medium Kow, medium volatility, medium water-soluble persistent and dense organics, medium to high water-soluble, medium to low Kd inorganic complexes and free ions: *TCE, vinyl chloride, BTEX, ethers (e.g., methyl-tert-butyl ether, MTBE), phenols, atrazine, soluble metal complexes, colloidal metals*
Air	Volatile organics, particle-associated organics and inorganics: *Chlorinated solvents, light hydrocarbons, freons, BTEX, and particle-bound PCBs, dioxins, and metals*
Aquatic biota	High Kow, persistent organics: *PCBs, chlorinated pesticides, PAHs, methyl mercury*
Terrestrial biota	High Kow, persistent organics, bioaccumulated metals and radionuclides: *PCBs, DDT, mercury, lead, radium*

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The general grouping scheme in Table 3-4 is based on relative ranges of values for a number of important physical constants that determine the behavior of chemicals in the environment (including constants identified in Table 3-3). These ranges have been drawn from information on a wide variety of chemicals in order to illustrate an approach that can be used to group chemicals. Physical properties are given for several chemicals in Table 3-5; these example chemicals were selected to illustrate a wide range of values for the parameters discussed above.

Groups of chemicals that might be expected to be distributed to various environmental compartments (or media) as described above are illustrated in Table 3-6. These examples assume that sufficient time has passed for transport and system equilibration to occur. In some cases, such as deposition in aquatic sediments or transport through the food chain, this can take from months to years following an initial release of contaminants. By the same token, after an extended time, chemicals from a variety of different sources would be expected to ultimately reach similar environmental sinks. In cumulative risk assessments, it might be important to examine when these chemical movements would occur.

An example that illustrates how available information can be evaluated to determine what release processes and receiving media are most significant, considering past, current, and possible future releases, is offered in Text Box 3-7 (U.S. EPA, 2004c). Note that both the transfer of contaminants from one medium to another and environmental transformation are considered as part of the fate and transport evaluation.

In this example, the identification of the most significant sources leading to air contamination would involve consideration of information such as chemical form, physical-chemical properties (such as volatility), transformation, partitioning and mobility, persistence, and bio-uptake (including combined environmental fate and co-location). A quantitative fate and transport analysis is not conducted until later in the process (see Section 3.3.2.3); the intent at this point is to identify what media are receiving chemicals from the identified source (or sources). A number of tools and databases exist to support the evaluation of contaminant fate and transport. Selected highlights are offered in the cumulative risk toolbox in Appendix A.

Example of Possible Release Sources *(Text Box 3-7)*

To assess cumulative hazards of urban air toxics in the Chicago area, it was determined to be most useful to focus on multiple releases to air. Most source release data identified in an environmental loadings profile were for point releases; some data for area and mobile sources of air pollution were also available. Although data on discharges to surface waters could have been obtained, the potential for exposure through this source was considered more limited than for exposure through source releases to air. Similarly, because the source of tap water for much of the Chicago area is Lake Michigan, very limited (if any) exposure to groundwater exists via the drinking-water pathway. Finally, if a chemical spill occurred, cleanup was assumed to be relatively quick (following environmental regulations) when compared to other sources of exposure, so the potential for exposure to soil contaminated from a recent spill was considered very low.

One study finding was that relatively few point sources account for a high percentage of point-source hazards, suggesting that such sources provide a logical starting point for hazard management actions. In summary, focusing on suspected predominant sources can reduce the complexity and cost of the initial exposure assessments.

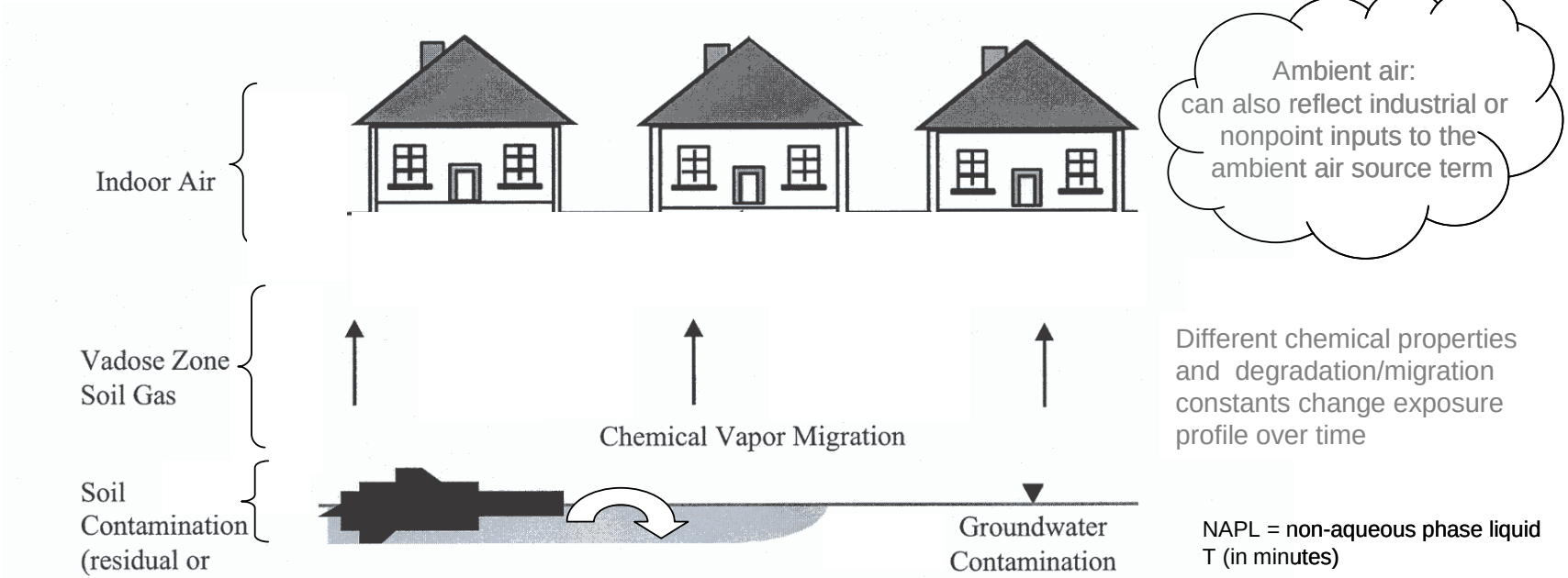
For a given set of chemicals, only one medium might be contaminated under current conditions (e.g., site soil), but different media could be affected over time, e.g., as contaminants migrate to groundwater or surface water or are taken up in food products. Thus, other time-related considerations include differential travel times for multiple contaminants (e.g., migrating to groundwater) and for subsequent transport to an exposure point. In addition, interactions could influence the mobility of multiple chemicals present together, or interactions could occur among transformation products that are formed over time. These concepts of migration and transformation are illustrated by the differential toxicity of the degradation products of trichloroethylene

(TCE), notably 1,2-dichloroethylene and vinyl chloride, as was described in section 3.3.2.1 and as shown in Table 3-1. This concept is illustrated by an example in Figures 3-5 and 3-6, which shows that while the exposure profile changes in the temporal scale, so can the toxicity profile. For example, in a chlorinated plume, the parent compound tetrachloroethylene degrading through TCE to vinyl chloride can actually pose greater risk later (as the plume contaminants gradually degrade) both in groundwater and via the passive (indoor air) inhalation pathway as the more volatile vinyl chloride preferentially passes through the vadose zone and could become trapped closer to the receptors at the land surface.

Cumulative assessments may also evaluate combined sources and joint environmental fate and transport. Although some traditional assessments do consider multiple sources and multiple contaminants, differential partitioning into environmental media over time is often overlooked. As examples:

- dioxin congeners can partition differently between soil and vegetation;
- site-specific soil characteristics will determine the extent of volatilization for volatile organic compounds;
- the extent of vegetative cover determines soil runoff into surface water; and
- weathering can change the composition of an original contaminant mixture.

The composition of spilled oil has been shown to change over time, as has that of the toxaphene mixture described in Text Box 3-8 (from U.S. EPA, 1997d). Methods to account for differential partitioning continue to evolve. For example, the EPA soil screening guidance considers the potential for individual soil contaminants to migrate to groundwater, based on a simple soil screening-level partitioning equation and the use of either of two dilution attenuation factors (U.S. EPA, 1996a). This approach could be



	First-Order GW [a]	T_0 Concentration (ppm)			T_1 Concentration (ppm)			T_{10} Concentration (ppm)		
	Decay Constant [b]	Soil	GW	IA	Soil	GW	IA	Soil	GW	IA
PCE	<0.1-110 (avg 4)	100	5.2	ND	10	0.1	4	ND	ND	3.5
TCE	<0.1-90 (avg 1)	30	6.7	ND	3	2.5	2.4	ND	0.0003	0.5
VC [c]	<0.2-20 (avg 0.6)	0.5	2	ND	0.05	1.1	3.1	ND	0.005	ND

a Abbreviations as follows: avg = average. GW = ground water. IA = indoor air. ND = not detectable.
PCE = perchloroethylene (tetrachloroethene). ppm = parts per million. T = time. TCE = trichloroethylene. VC = vinyl chloride.
b U.S. EPA 1998. Technical Protocol for Evaluating Natural Attenuation of Chlorinated Solvents in Ground Water.
Office of Research and Development, Washington DC. EPA/600/R-98/128. September.
c Assuming natural attenuation and degradation are occuring all the way through ethane, excess VC is not generated, as shown here. However, if incomplete degradation occurs, VC may accumulate, and the reductions shown here may not occur.

FIGURE 3-5

Example Changes in Exposure Profile from Degradation and Partitioning

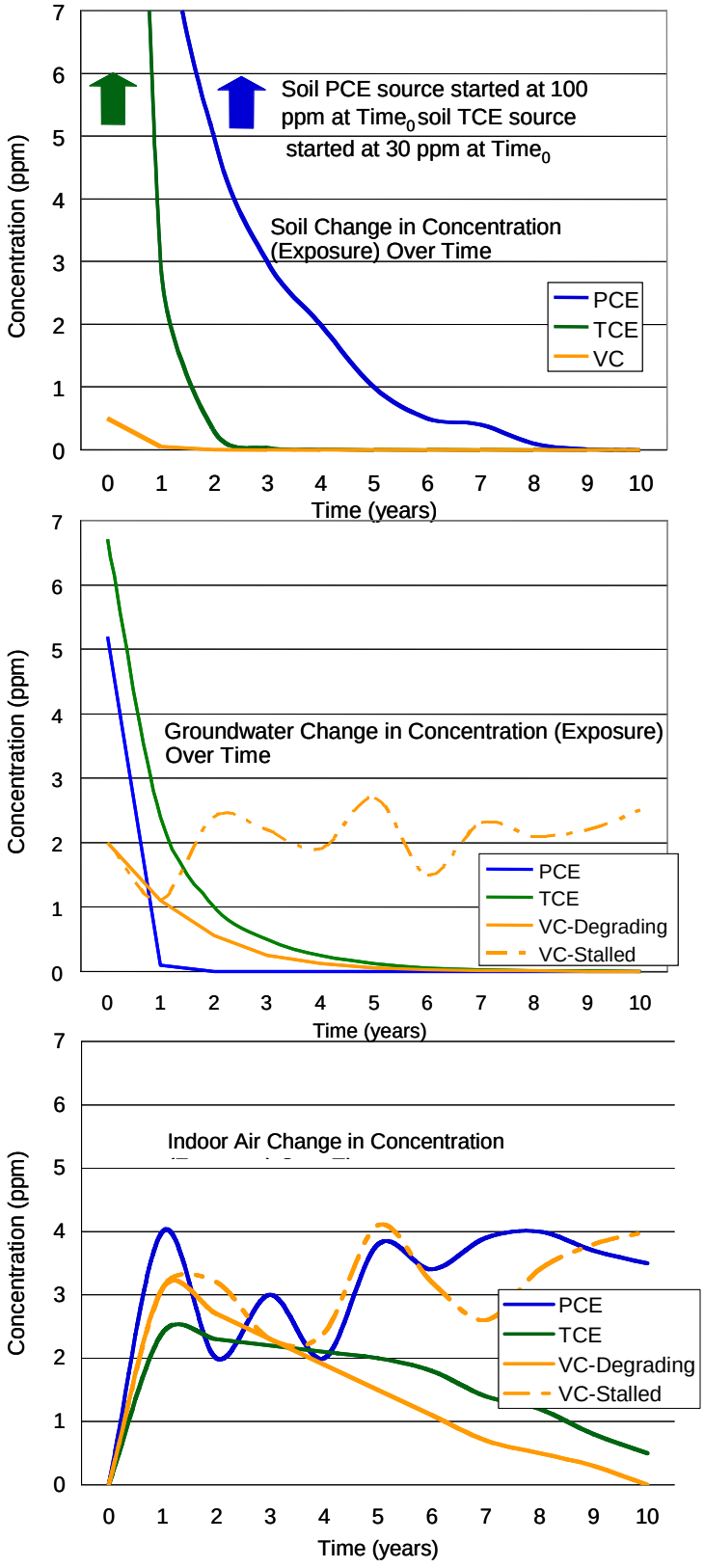


FIGURE 3-6

Illustration of Changing Media Concentrations Affecting Potential Exposures

used for screening multiple contaminants to support grouping for a cumulative risk assessment.

3.3.2.3. Exposure Points and Routes — The next phase of the exposure assessment involves identifying who is likely to come in contact with chemical pollutants, where, and by what route(s) of exposure. The exposure points (the geographical locations where people could come in contact with the chemicals) and routes (ingestion, inhalation, and dermal absorption) are identified for each exposure pathway, and then integrated for the cumulative assessment. It is important to consider also interactions that might enhance exposures or associated effects and to evaluate when these exposures may occur.

Weathering Example: Toxaphene *(Text Box 3-8)*

Until the 1970's, toxaphene was the most heavily used pesticide in the United States. It was formulated using multiple ingredients, and their relative amounts change after the pesticide is released because of differential partitioning and transformation processes in air, water, and soil. (The soil half-life can be 1 to 14 years.) Over time these components continue to change, so the composition of weathered toxaphene differs significantly from the original mixture. Samples collected from different sources might also differ, depending on the location-specific environmental processes to which the original mixtures were exposed. For example, weathered toxaphene in an anaerobic soil does not resemble that in an aerobic soil, and that in an air sample from the Arctic does not resemble residues found in the blubber of an Arctic seal. Some components of this environmental mixture might not be routinely identified through standard analyses. Site-specific partitioning and transformation processes must then be considered to properly assess what compounds could be present at a given time. It is also important to link this information with the toxicity evaluation, because weathered compounds will also exhibit different toxicities from the original mixture components.

Non-chemical factors can change exposures and potentially influence the toxicokinetics (e.g., rate of disposition to a target tissue). The higher ventilation rates for joggers running near an emission source are an example of an exposure factor that influences exposure. This, in turn, could increase the rate at which he or she inhales airborne chemicals. Co-exposure to toluene and noise offers an example of synergism because this organic compound damages the auditory system and can also potentiate additional damage by noise, a physical stressor, beyond what would be expected by the two acting separately (U.S. EPA, 2003e).

At this point of the assessment, available information is integrated to link the sources of multiple chemicals, their releases and fate/transport, the exposure points for likely receptors, and the exposure routes (U.S. EPA, 1989a). The focus is on exposure pathways that are currently complete or are likely to become complete. Thus, relevant time frames of these exposures are appropriate to consider at this point, to guide the evaluation of the frequency, duration, intensity, and possible overlaps of exposures to multiple chemicals, as well as the sequence of those exposures. The level of detail needed in the exposure assessment with respect to exposure overlaps should be evaluated with the dose-response analyst. The dose-response analyst may provide information on whether the overlap of exposures co-occurring on the same day within a week, a month, or a year matters toxicologically.

Information on background exposure levels to common environmental contaminants can be important to cumulative assessments. A key resource for this information is available through the National Human Exposure Assessment Survey (NHEXAS) program (U.S. EPA, 2004d). That program was designed to address some of the limitations of single-chemical and single-media exposure studies as one of its goals is to test and evaluate different techniques and design approaches for performing multimedia, multipathway human exposure studies. The NHEXAS data can be used as baseline information for exposure assessments to indicate if specific populations are exposed to increased levels of environmental contaminants. These data are available in the Human Exposure Database System (HEDS), which contains chemical

measurements, questionnaire responses, documents, and other information related to EPA studies of human exposures to environmental contaminants (see Appendix A).

To evaluate what chemicals might coexist at places where receptors are, or could be, exposed, site-related contaminants can be grouped by considering when they might coexist in space and time. This grouping should reflect transport and fate considerations, including transformation, that are appropriate for the time intervals studied. Minimally, four groups are defined to guide this evaluation of possible exposures to multiple chemicals in various environmental media over time, as shown in Text Box 3-9. Clearly, for analyses that evaluate multiple chemicals, there can be multiple media and multiple time points to evaluate. Assuming that these chemicals co-occur in media that individuals in the community may contact, these exposure groupings can then be linked with toxicity information to assess joint impacts, as described in Chapter 4. Note that these can be evaluated as potential doses. (In refined cumulative exposure assessments, toxicokinetic and toxicodynamic information could be used to provide a comprehensive understanding of the magnitude of tissue doses over time (see Sections 3.3.3 and 3.3.4).

Chemical Groupings by Coexistence in Media/Time
(Text Box 3-9)

	Media	
Time	Same	Different
Same	Group 1	Group 3
Different	Group 2	Group 4

The Agency identifies several time-course issues in the *Framework for Cumulative Risk* document (U.S. EPA, 2003a). Certain chemical pairs can demonstrate different toxicity depending on the sequence of exposures, with cancer initiators and promoters being the classic example; exposure to a promoter has no effect if it occurs prior to exposure to an initiator. This illustrates the same media/different time and

different media/different time concepts indicated above. Examples of chemical pairs for which the toxicological effect is influenced by exposure timing are shown in Text Box 3-10. Specific joint toxicity issues are discussed in Chapter 4.

Examples of Chemical Pairs Influenced by Exposure Timing *(Text Box 3-10)*

Benzo[a]pyrene (BaP) and tris(2-ethylhexyl) phosphate (TPA) are an initiator/promoter pair:

TPA does not have a tumorigenic effect in mouse skin assays, but applying it after initiation with BaP, greatly enhanced tumorigenic activity (Verma et al., 1985).

Cadmium and lead illustrate antagonism:

Initial exposure to cadmium has been shown to decrease the absorption of lead following subsequent exposure, which has the effect of decreasing the blood lead level and causing less-than-additive hematopoetic toxicity (other data suggest different joint toxicity, as affected by the order of exposure, from ATSDR, 2004).

Several commercial exposure models have been developed to capture the time aspects of exposures, and several tools are indicated in Appendix A.

3.3.3. Exposure Quantification. Outputs of fate and transport models, such as from air dispersion modeling, can be used to define the temporal and spatial distribution of chemicals needed to quantify human exposures. When monitoring data are available, estimates of exposure could primarily be based on those measures of contaminant concentrations in the environment, as indicated by the type and quality of the data.

Cumulative exposures to a given population could be estimated for various exposure pathways and for contaminants of interest to the community. For this assessment, as many of the following data as are applicable are used to determine cumulative exposures to a given population:

- body burdens (e.g., concentrations of lead in blood)
- measured concentrations in air, groundwater, surface water, soil, sediments, and food or
- modeled concentrations in the ambient environment (not linked to sources).

Prior exposures could also be considered if data are available.

Such a total exposure approach could result in certain sources being essentially unidentifiable and might include non-industrial contaminant sources such as consumer products, environmental tobacco smoke, radon, and pesticide residues on foods. However, the end result could be comprehensive exposure estimates for the population, which would include environmental contaminants that are showing up in the monitoring data. Some stakeholders might desire such an assessment, but it would typically be beyond the scope of a contaminated site assessment project. The assessment may identify an evaluation of unknown sources of contaminants as a potentially important research need. The information offered in this report and many other resources can be used to support such complementary analyses by other groups, as desired.

3.3.3.1. Exposure Point Concentrations — The concentrations of chemicals to which people are, or could be, exposed over the time period of interest can be represented by a combination of monitoring data and transport and fate models. To review the concepts discussed in earlier sections, models are the only way future concentrations can be estimated. Models are used to fill gaps in data for current conditions.

Models can be applied at different levels during a cumulative risk analysis, beginning with a simple screen to winnow down the list of chemicals of concern and exposure pathways by eliminating those clearly not expected to contribute to adverse effects. Using known (not missing) information, this screen reduces the list of chemicals included in the more detailed analysis, thus facilitating a more focused analysis. Simple fugacity models can be used to predict movement and phase change in the environment, for example, to identify which chemicals volatilize, stay soil bound, lodge

in fat of fish or other food species. Environmental breakdown products should be identified as indicated by the data or acknowledged as potentially present where those data do not exist. Rare events that might result in different combinations of chemicals being released to the environment at higher levels may be considered.

The next step could be to rank mixtures by defining the chemical and exposure combinations of main concern and those mixtures that are unlikely to pose a problem. Exposures to the population of concern could be quantified assuming steady state, also indicating expected departures from steady state conditions. If needed, a final iteration would involve applying more detailed dynamic fate and transport models to predict time-varying concentrations in each media, also including spatial changes in exposure concentrations.

For more precision, this kind of exposure modeling over time could consider physiological factors as indicators of likely overlap of internal doses and of possible damping of external exposure fluctuations (internal overlaps are discussed in Section 3.3.3.4). Quantitative estimates of exposure would then be determined over these different time periods. Selected exposure models that can be used to support these exposure analyses are included in the cumulative risk toolbox in Appendix A.

3.3.3.2. Intake Estimates — Using measured and predicted estimates of the concentrations of multiple chemicals at each exposure point of interest, exposure factors relevant to each receptor are then applied to calculate pathway-specific intakes. These intakes are calculated using equations that generally include intake variables for media concentrations (over time), the contact rate, exposure frequency, exposure duration, body weight, and exposure averaging time, as indicated in the basic EPA

guidance (U.S. EPA, 1989a). The *Exposure Factors Handbook* (U.S. EPA, 1997c) identifies specific intake rates for air, water, and foods. These equations are then adapted to the specific exposure route: oral, inhalation, or dermal.

The general intake equation is:

$$\text{Intake (mg/kg-day)} = \frac{C \times IR \times EF \times ED}{BW \times AT} \quad (3\text{-}1)$$

where:

C = concentration (i.e., exposure point concentration) (e.g., mg/L for water)

IR = intake rate (e.g., L/day for water)

EF = exposure frequency (days/year)

ED = exposure duration (years)

BW = body weight (kg)

AT = averaging time (period over which exposure is averaged, in days)

Community-specific exposure factors are preferred in calculating intakes, but generic values can be used for conservative screening-level analyses. The cumulative risk across all chemicals, media, and exposure routes will be estimated from these combined calculations linked with toxicity data. For example, rare events that might result in different combinations of chemicals could yield different exposure point concentrations that would not normally be evaluated but would be included in the exposure assessment.

An example scenario was developed for current and future land use at a hypothetical contaminated site to illustrate the evaluation of multiple pathways and degradation products. As shown in Table 3-7, receptors under current conditions are assumed to be an on-site maintenance worker and off-site resident. Exposures are

1

TABLE 3-7

Example of Cumulative Exposures for Current Land Use*

Chemicals/ Transformation Products	Exposure Medium and Location[c,d]	Chemical Intakes (mg/kg-day)		
		Ingestion	Inhalation	Dermal
On-Site Maintenance Worker				
Tetrachloroethylene	Site soils	2×10^{-5}		5×10^{-7}
	Ambient air		5×10^{-6}	
Chlorine	Ambient air		7×10^{-7}	
Trichloroethane	Site soils	4×10^{-8}		8×10^{-10}
	Ambient air		3×10^{-9}	
Vinyl chloride	Ambient air		6×10^{-10}	
Benzo(a)pyrene	Site soils	8×10^{-4}		7×10^{-6}
	Ambient air		2×10^{-5}	
	Surface soils	1×10^{-6}		2×10^{-8}
Anthracene	Site soils	2×10^{-7}		4×10^{-9}
	Ambient air		6×10^{-8}	
	Surface soils	9×10^{-10}		3×10^{-11}
PCBs (as Aroclor 1254)	Site soils	2×10^{-5}		2×10^{-7}
	Ambient air		6×10^{-6}	
	Surface soils	7×10^{-7}		5×10^{-9}
Aldrin	Site soils	2×10^{-3}		4×10^{-5}
	Ambient air		1×10^{-5}	
	Surface soils	5×10^{-5}		4×10^{-7}
Dieldrin	Site soils	1×10^{-6}		1×10^{-8}
	Ambient air		4×10^{-7}	
	Surface soils	2×10^{-6}		4×10^{-10}

2

TABLE 3-7 cont.

Chemicals / Transformation Products	Exposure Medium and Location[c,d]	Chemical Intakes (mg/kg-day)		
		Ingestion	Inhalation	Dermal
Arsenic	Site soils	8×10^{-6}		2×10^{-8}
	Ambient air		3×10^{-7}	
	Surface soils	5×10^{-7}		9×10^{-10}
Chromium	Site soils	8×10^{-7}		2×10^{-9}
	Ambient air		5×10^{-8}	
	Surface soils	7×10^{-9}		3×10^{-11}
Lead	Site soils	3×10^{-6}		8×10^{-8}
	Ambient air		2×10^{-7}	
	Surface soils	9×10^{-9}		1×10^{-10}
Mercury	Site soils	4×10^{-5}		3×10^{-7}
	Ambient air		8×10^{-6}	
	Surface soils	6×10^{-7}		2×10^{-9}
Off-Site Resident				
Tetrachloroethylene	Aquifer - tap water	1×10^{-5}		2×10^{-7}
	Vapors from shower		6×10^{-8}	
Chloroform	Aquifer - tap water	9×10^{-6}		3×10^{-7}
Chlorine	Vapors from shower		5×10^{-7}	
Trichloroethane	Aquifer - tap water	7×10^{-8}		2×10^{-10}
	Vapors from shower		4×10^{-9}	
Vinyl chloride	Vapors from shower		9×10^{-10}	

*The example scenarios assume exposures at the site under current conditions, e.g., degradation products are identified for chemicals that undergo conversion on the order of hours or days. The source release is assumed to be a spill to surface soils with subsequent leaching to subsurface soils and groundwater. The exposure point concentrations are assumed to be unit concentrations of 1 mg/kg, 1 mg/m^3, or 1 mg/L for calculating intakes of soil/biota, air, or water, respectively. The exposure media are site soils at or beneath the spill location, ambient air from resuspended particulate matter, surface soils from deposition of resuspended particulate matter, in groundwater at the tap, and water vapors from showering. Estimates will depend on the default and/or site-specific exposure factors used in the intake equations.

assumed to occur via several pathways following a chemical spill. To account for changes over time, cumulative intakes are calculated for exposures to original chemicals as well as degradation products that can result from relatively rapid conversion. Intakes for ingestion, inhalation, and/or dermal contact are calculated for applicable media and are then used to calculate cumulative risk estimates in the risk characterization step.

For a future land use scenario, exposure assessments would be appropriate for on-site residents and an off-site recreational visitor. As noted in Table 3-8, exposures occur by several pathways that reflect the much longer time frame (e.g., 20 years). Again, to account for changes over time, cumulative intakes are calculated for exposure to chemicals plus conversion products that result from relatively slow degradation (on the order of months or years). Volatile organics in surface or near-surface soils are assumed to have dissipated so are not considered in future exposure assessments. Intakes for the exposure routes of ingestion, inhalation, and/or dermal contact are calculated for applicable media and are then used to calculate cumulative risk estimates in the risk characterization step.

3.3.3.3. Calendar Approach — While no Agency-wide standardized procedure exists for detailed consideration of exposure timing in dose/response assessment, the Office of Pesticide Policy provides an approach in *General Principles for Performing Aggregate Exposure and Risk Assessments* (U.S. EPA, 2001a). Figure 3-7 provides an overview of their *calendar approach*. The calendar approach estimates sequential, daily chemical exposures by linking episodic exposures (e.g., seasonal exposures to pesticides through surface water contact following residential lawn applications of

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TABLE 3-8

Example of Cumulative Exposures for Future Land Use*

Chemicals / Transformation Products	Exposure Medium and Location	Chemical Intakes (mg/kg-day)		
		Ingestion	Inhalation	Dermal
On-Site Resident				
Benzo(a)pyrene	Site soils	3×10^{-4}		2×10^{-8}
	Ambient air		2×10^{-5}	
	Surface soils	1×10^{-6}		2×10^{-10}
Anthracene	Site soils	2×10^{-3}		5×10^{-4}
	Ambient air		6×10^{-5}	
	Surface soils	8×10^{-6}		2×10^{-7}
PCBs (as Aroclor 1254)	Site soils	2×10^{-6}		6×10^{-7}
	Ambient air		5×10^{-5}	
	Surface soils	4×10^{-8}		2×10^{-9}
Dieldrin	Site soils	1×10^{-6}		2×10^{-8}
	Ambient air		9×10^{-6}	
	Surface soils	3×10^{-8}		2×10^{-10}
Arsenic	Site soils	9×10^{-3}		7×10^{-7}
	Ambient air		1×10^{-5}	
	Surface soils	2×10^{-6}		6×10^{-9}
Chromium	Site soils	5×10^{-3}		2×10^{-5}
	Ambient air		7×10^{-4}	
	Surface soils	2×10^{-5}		8×10^{-7}
Lead	Site soils	8×10^{-3}		3×10^{-7}
	Ambient air		4×10^{-4}	
	Surface soils	9×10^{-5}		2×10^{-9}
Mercury	Site soils	1×10^{-6}		5×10^{-8}
	Ambient air		6×10^{-6}	
	Surface soils	2×10^{-7}		5×10^{-10}
Benzo(a)pyrene	Surface runoff to lake	1×10^{-8}		2×10^{-11}

2

TABLE 3-8 cont.

Chemicals / Transformation Products	Exposure Medium and Location	Chemical Intakes (mg/kg-day)		
		Ingestion	Inhalation	Dermal
Off-Site Recreational Visitor				
Anthracene	Surface runoff to lake	4×10^{-7}		1×10^{-10}
PCBs (as Aroclor 1254)	Surface runoff to lake	9×10^{-9}		4×10^{-12}
	Fish in lake	5×10^{-6}		
Dieldrin	Surface runoff to lake	2×10^{-9}		8×10^{-12}
Arsenic	Surface runoff to lake	3×10^{-7}		6×10^{-10}
Chromium	Surface runoff to lake	8×10^{-8}		2×10^{-11}
Lead	Surface runoff to lake	1×10^{-7}		7×10^{-10}
Mercury	Surface runoff to lake	2×10^{-8}		5×10^{-11}
Methylmercury	Fish in lake	3×10^{-5}		

* These example scenarios assume exposures at the site under future conditions, e.g., degradation products are identified for chemicals that undergo conversion on the order of months or years. In addition, TCE and PCE in surface soils are assumed to have completely volatilized by the time the future land use scenario begins, with aldrin having been converted fairly rapidly to dieldrin. The source release is assumed to be a spill to surface soils with subsequent leaching to subsurface soils and groundwater. The exposure point concentrations are assumed to be unit concentrations of 1 mg/kg, 1 mg/m^3, or 1 mg/L, for calculating intakes of soil/biota, air, or water, respectively. The exposure media are site soils at and beneath the spill location, ambient air from resuspended particulate matter, surface soils from deposition of resuspended particulate matter, surface water, and lake fish. Estimates will depend on the default and/or site-specific exposure factors used in the intake equations.

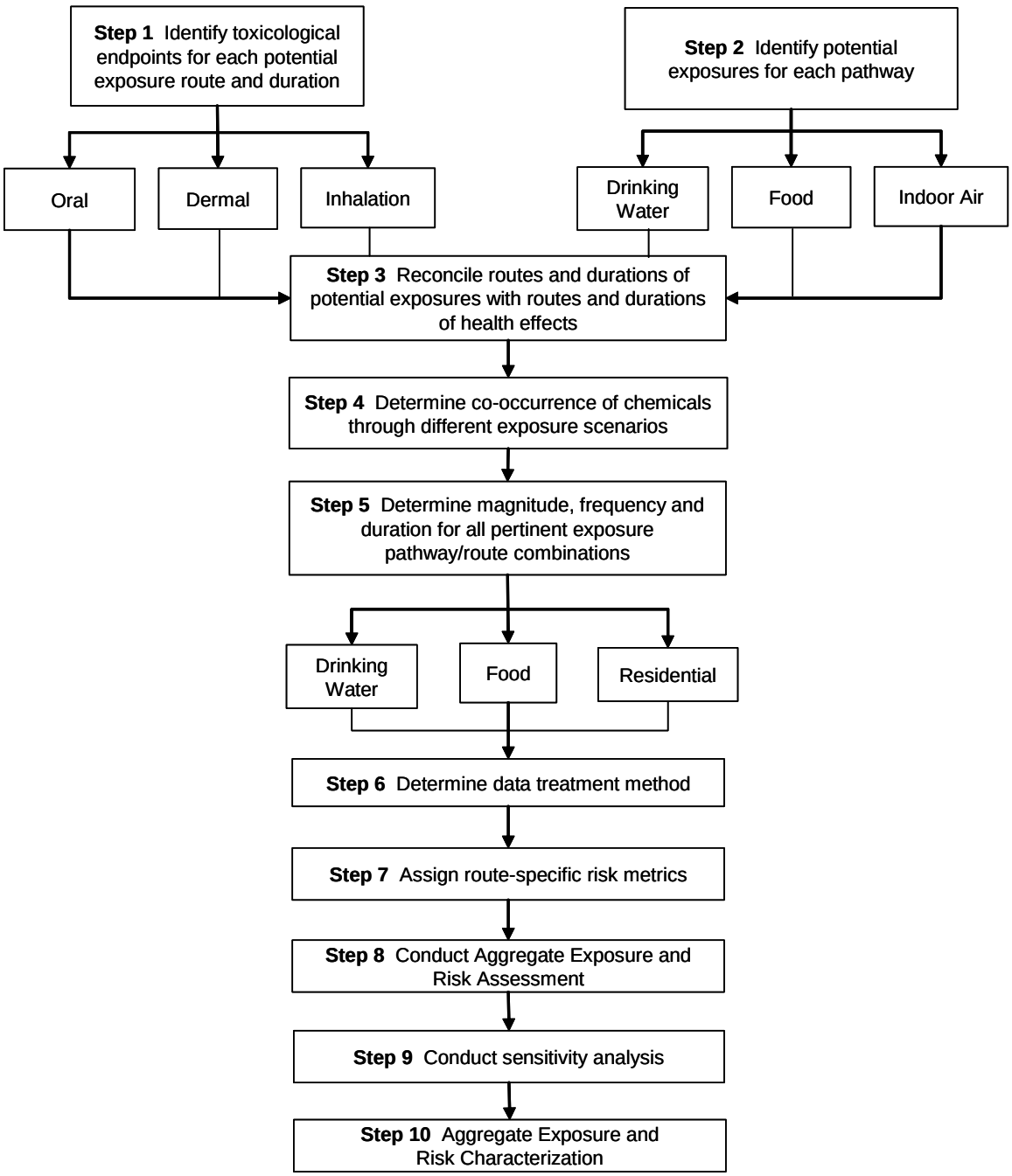


FIGURE 3-7

Ten Steps in Performing Aggregate Exposure and Risk Assessment
(Adapted from U.S. EPA, 2001a)

pesticides in the spring and summer) with routine exposures (e.g., contaminants in the food supply). Figure 3-8 illustrates the pattern of results that may be predicted using this approach. The discussion that follows adapts this approach, which covers aggregate exposures, to cumulative exposure practices. This discussion focuses on Steps 1-6, followed by additional information about the calendar approach.

The first and third steps are conducted by both the dose-response analyst and the exposure analyst. The goal of these steps is to identify the health effect(s) associated with each chemical or group of chemicals identified. This includes an analysis of which exposure route(s) and exposure duration(s) produced the effect(s) and a step (step 3) to ensure that the dose-response assessment and the exposure assessment are concordant. A previous document (U.S. EPA, 1999e) describes five general durations of exposure considered:

- acute – in a cumulative assessment this could include one-day exposures through oral (food and water pathways, which reflects distribution of daily food consumption and daily water residue values), inhalation (atmospheric concentrations) and dermal routes, which reflects daily water and soil residue values)
- short-term – could include 1- to 30-day exposure scenarios
- intermediate-term – could include 30- to 180-day exposure scenarios
- chronic/long-term – could include exposures of greater than six months in duration, and
- cancer – lifetime assessment.

Following the identification of the toxicologic endpoint(s), duration of exposure(s), exposure scenario(s) of concern, Step 4 requires the analyst to examine residential exposures that might occur to potential receptors (e.g., home pesticide or herbicide) (U.S. EPA, 2001a). This is accomplished by appropriately combining information about

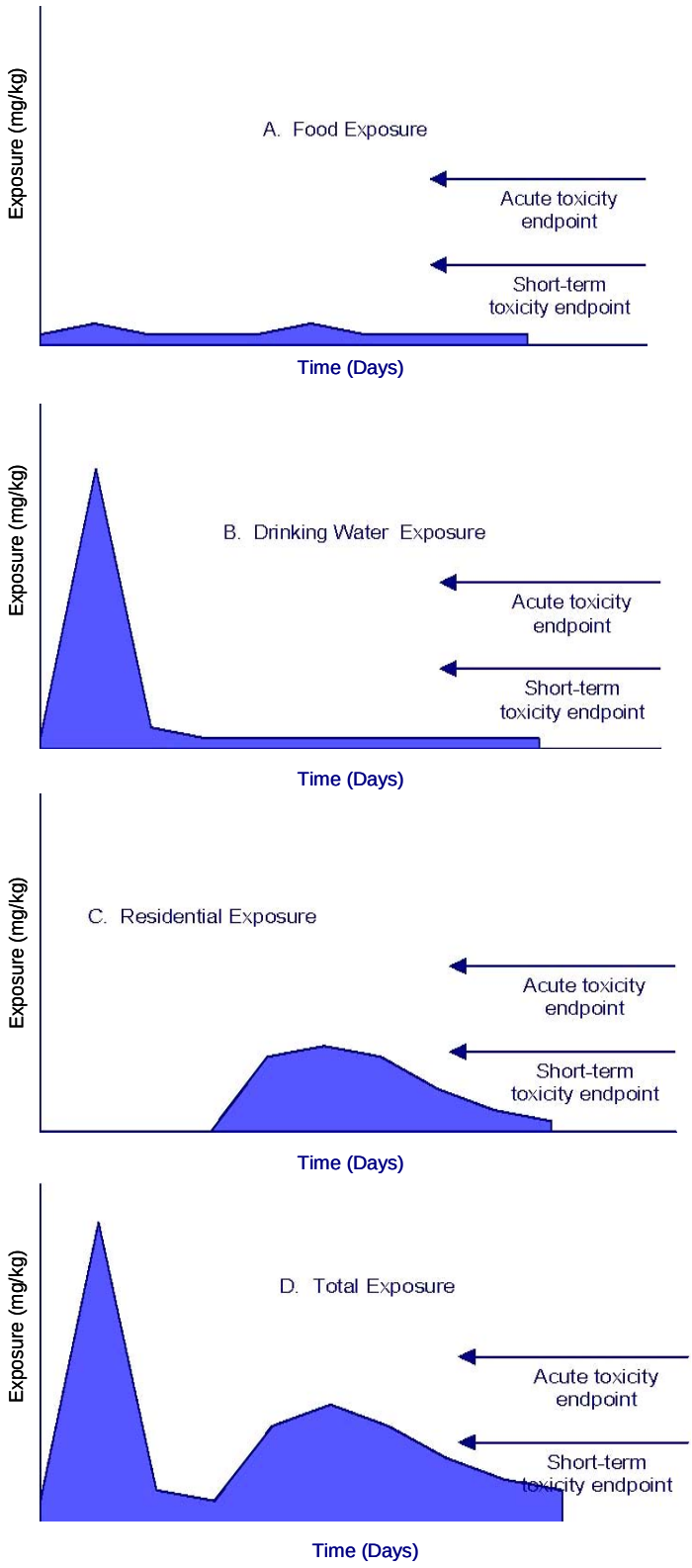


FIGURE 3-8

Pathway-specific and Combined Exposure to a Single Hypothetical Chemical

a potentially exposed individual's demographic (e.g., age, gender, and racial/ethnic background), temporal (season), and spatial (region of the country) characteristics.

A cumulative exposure assessment could undertake the same steps combining national data to estimate background exposures with site-specific data to estimate local exposures. This point is illustrated using a single chemical exposure. Methylmercury exposures can result from consumption of locally-caught fish and commercial fish (i.e., two different sources of fish). An analysis could examine the correlation between consumption rates of locally-caught and commercially-caught fish and use both average local fish methylmercury levels and average commercial fish methylmercury levels to estimate methylmercury exposures in individuals consuming a mix of these fish. Such an analysis could also capture seasonal consumption patterns (and associated exposure patterns) of locally-caught fish. Furthermore, U.S. EPA (1999e) suggests that distributional data analyses (as opposed to a point estimate approach) are preferred because this tool allows an aggregate exposure analyst to more fully evaluate exposure and resulting risk across the entire population, not just the exposure of a single, high-end individual.

Steps 5 and 6 integrate the magnitude, frequency, and duration of exposure for all relevant pathway and route combinations. Consequently, the hypothetical individual's temporal, spatial, demographic, and behavioral exposure characteristics need to be considered for each relevant duration in the assessment. This results in a calendar approach to the exposure assessment because the timing of the multi-route exposure relative to each other is critical to the evaluation of the health endpoint.

Figure 3-8 (adapted from a figure in U.S. EPA, 2001a) illustrates the combination of exposure pathways over time (in this case, days) for a single chemical.

Exposures to two or more chemicals can overlap if the chemicals coexist in the same environmental medium during the same exposure period of interest. If there are multiple pathways that involve different chemicals, independence should not be assumed. Instead, joint exposure should be evaluated for potential overlap of potential doses (e.g., chemicals in local fish and air that result in overlapping potential doses) and internal dose (including metabolites), for potential toxicological interactions, or for potential overlap of effects. Information on environmental fate is important input to this evaluation. For example, a screening-level comparison of Kd values in soil could be used to gauge the potential for simultaneous migration of a group of chemicals (see Table 3-3).

People can be exposed to chemicals at the same time but in different media. For example, exposure to inorganic mercury in soil and shellfish, to DBPs in drinking water and during showering, and to volatile organic compounds in indoor air (originating from a site or from the use of household or office products) could all be combined for a full cumulative assessment. Text Box 3-11 uses the chemical groupings based on coexistence in media and

Examples of Chemical Groupings by Coexistence in Media/Time
(Text Box 3-11)

Time \ ***Media***	Same	Different
Same	Group 1 Coexposures to mixture of DBPs via consumption of unheated tapwater	Group 3 Coexposures to volatile and non-volatile DBPs via inhalation while showering and consumption of unheated tapwater
Different	Group 2 exposures via contaminated drinking water to different pesticides with short environmental half-lives	Group 4 VOC exposures via inhalation due to temporary incinerator to remediate a site and, years later, exposures to metal mixture via consumption of contaminated groundwater

time to illustrate chemical combinations highlighted in this paragraph and other potential combinations.

3.3.3.4. Combining the Calendar Approach with Toxicokinetic Models — The calendar approach (U.S. EPA, 2001a) can be combined with toxicokinetic models to estimate tissue doses for mixture components over time. U.S. EPA (2001a) described a calendar approach that estimates daily exposures up to a full year. The calendar approach can be used to assess exposures resulting from seasonal activities such as timing of pesticide applications over a year or the timing of pesticide runoff during the year. Such an approach can also be used to evaluate exposures via indoor air, which could change seasonally. The approach integrates exposures by route using probabilistic[5] input data (e.g., this approach could integrate oral exposures that result from food intake, drinking water consumption, and soil ingestion). The approach predicts distributions of potential doses via different exposure routes (see Figure 3-7). Clearly, this type of approach is most useful for pollutant concentrations that vary over relatively short periods of time (daily or weekly).

Figure 3-8 illustrates the results of a multipathway exposure assessment using a calendar based approach. Panel A of Figure 3-8 shows that the potential doses of this hypothetical pesticide through food consumption are relatively constant over the period of time evaluated. Panel B shows that the potential doses of this hypothetical pesticide are generally low. However, the potential doses from this exposure pathway may be quite high during a fraction of the period of time evaluated. The high exposures through the consumption of private drinking water might be due to runoff of this pesticide from

[5] In probabilistic exposure assessments, the population's exposures are characterized by distributions of exposure factors and contaminant concentrations.

lawns or agricultural lands. Panel C illustrates a residential exposure. It suggests that there is no pesticide dose from this pathway during certain periods of time (e.g., winter months), but a relatively large dose during other periods of time. Panel D combines these three pathways of exposure showing the potential dose of the hypothetical pesticide for each day of the exposure duration evaluated.

U.S. EPA (2003b) conducted research to examine the feasibility of conducting a cumulative risk assessment for DBP mixtures by combining exposure modeling and physiologically-based toxicokinetic (PBTK) modeling. Initially, a comprehensive exposure modeling effort was implemented to estimate population-based exposures and absorbed doses for 13 major DBPs, incorporating parameters for chemical volatilization, human activity patterns, water use behaviors, ingestion characteristics, building characteristics, physiological measurements, and chemical concentrations in the water supply. Daily exposure estimates were made for an adult female and an adult male and for a child (age 6) of total absorbed doses inclusive of exposures via oral, dermal, and inhalation routes. Estimates were developed for 13 major DBPs, accounting for human activity patterns that affect contact time with drinking water (e.g., tap water consumed, time spent showering, building characteristics) and physicochemical properties of the DBPs (inhalation rates, skin permeability rates, blood:air partition coefficients, etc.). Combining daily exposure information with a toxicokinetic model provides additional insights into the exposures, including residual concentrations in the body. Figure 3-9 provides an overview (from a biological perspective) of the exposure metrics that can be used. Figure 3-10 illustrates how an exposure assessment model was linked with a PBTK model for DBPs to estimate the

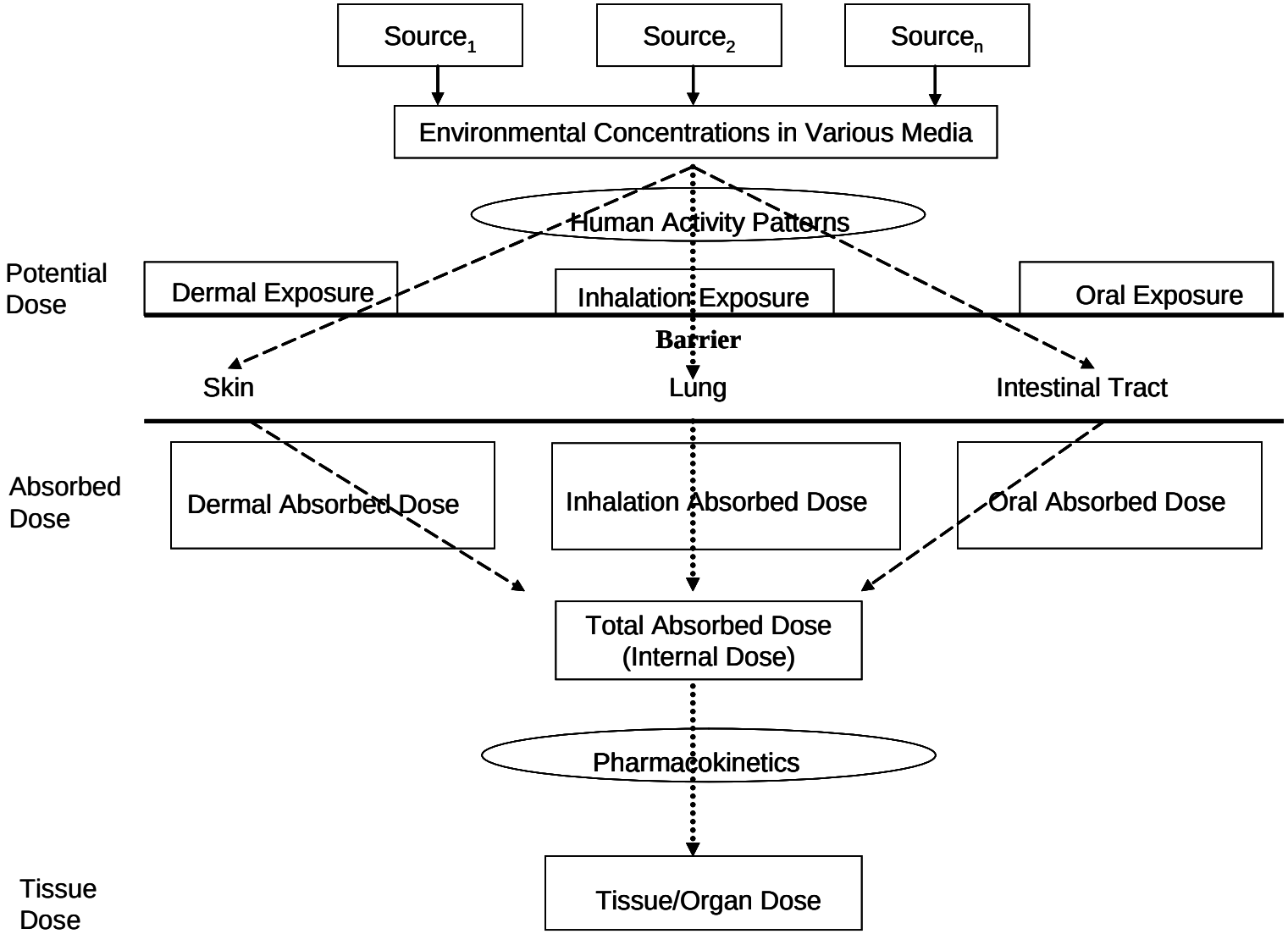


FIGURE 3-9

Dose Metrics for Environmental Contaminants (Source: U.S. EPA, 2003b)

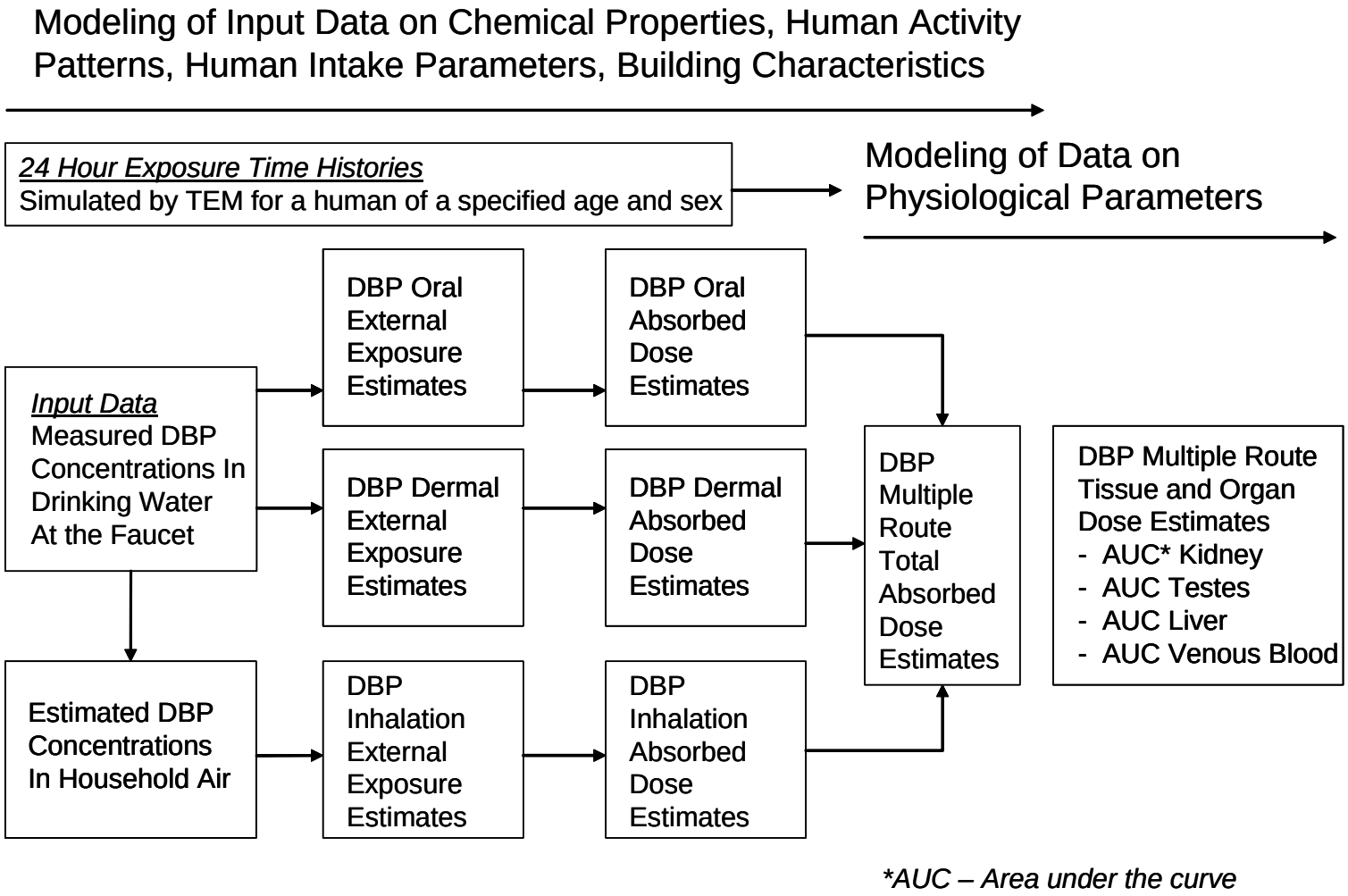


FIGURE 3-10

Linking Exposure Assessment Modeling with a PBTK Model for DBPs (Adapted from U.S. EPA, 2003b)

organ-specific doses (estimated as an area under the curve (AUC)). PBTK models provide a useful approach for integrating exposures across multiple exposure routes.

The kinetics of toxicants, when combined with exposure information, can be an important factor in determining whether chemicals will be present in the same target tissue within the body at the same time. While estimates of potential doses and the potential daily or seasonal variability in such doses are useful (based on the concentration of pollutants encountered in the environment, activity patterns, and intake rates), toxicokinetic models can provide refinements to this measure that may be critical to the cumulative exposure assessment. These refinements may include differential absorption of mixture components across boundaries, differences in the distribution of mixture components in the body, differential metabolism, and differences in elimination (e.g., clearance rates). Models can also be developed to estimate the kinetics of by-products of metabolism.

Figure 3-11 summarizes different levels of dose specificity that may be needed in a cumulative exposure assessment. Moving from level 1 to level 4 requires additional analytic detail. Depending on the chemicals being evaluated, levels 1 and 2 may require the use of dynamic fate and exposure models (e.g., the calendar approach).

Depending on the variability of the exposures in the pathways being evaluated, undertaking an analysis as depicted in levels 3 or 4 would likely require a dynamic exposure model that could simulate daily potential doses of multiple chemicals. Because of the chemical-specific nature of absorption, distribution, metabolism, and elimination, chemicals contacted at the same time may not remain in the tissues of the body for the same period of time. Thus, some compounds may be quickly eliminated

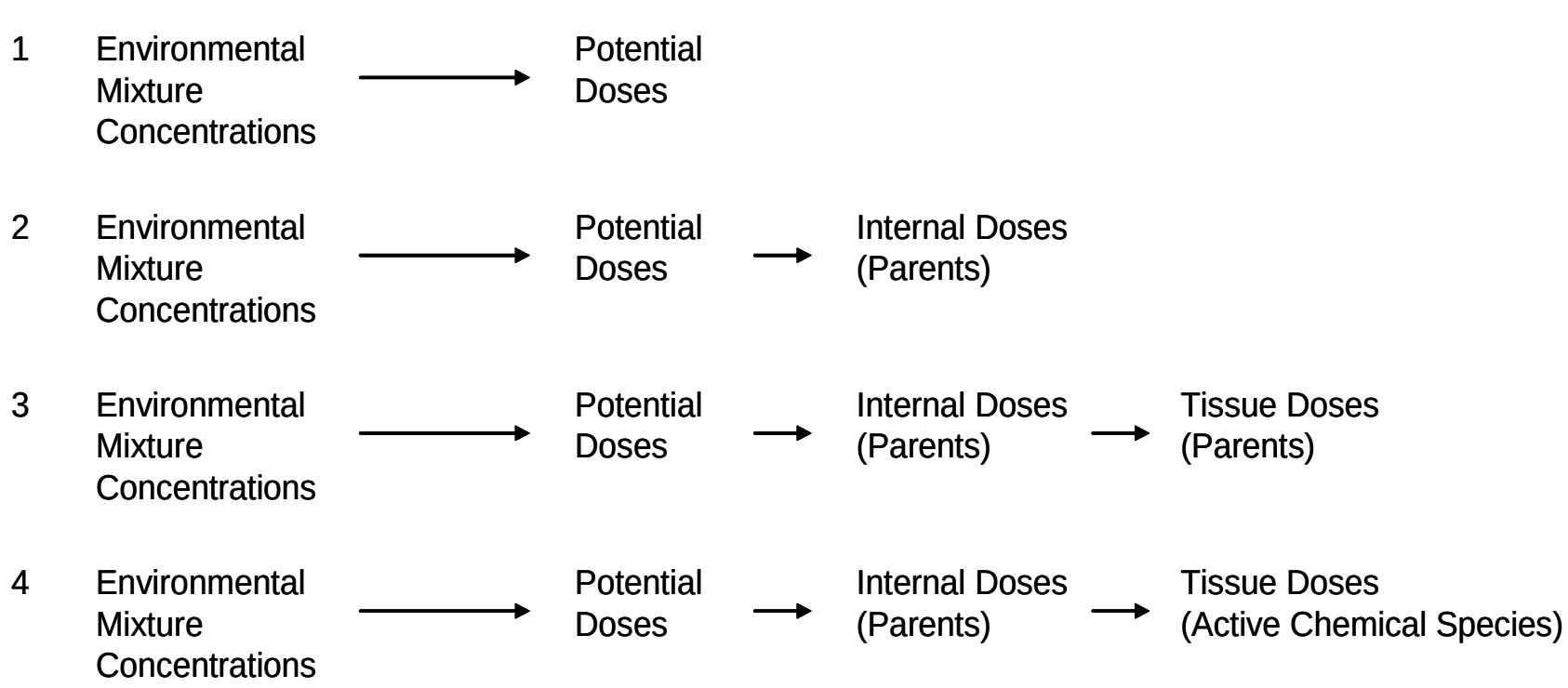


FIGURE 3-11

Levels of Dose Specificity that Can Be Estimated in a Cumulative Exposure Assessment

and others may be slowly eliminated resulting in prolonged tissue exposure. Figure 3-12 builds upon Panel D of Figure 3-8. It illustrates the target organ doses that correspond to the cumulative exposure depicted in panel A depend on whether the chemical is rapidly eliminated (panel B) or slowly eliminated (panel C). Figure 3-13 illustrates the different retention times exhibited by Chromium (III), Chromium (VI), and tritium. The disposition of chemicals absorbed through different exposure routes may differ. Undertaking an analysis as depicted in levels 3 or 4 (Figure 3-11) may be needed to determine if the exposures through different routes result in overlapping internal doses. The analyses depicted in levels 3 and 4 require a thorough understanding of toxicokinetic conditions. Level 3 estimates concentrations of the parent compounds in the target tissues over time. Level 4 requires knowledge of whether the compounds are toxic in their parent form or as metabolites and would predict concentrations of the toxicologically active chemical species in the target tissue over time.

In summary, doses may be considered at different levels of specificity. Each is potentially useful and differentially resource-intensive. The level of detail selected in the analysis should be determined through consultation with the dose-response analyst. The dose-response analysis may provide information demonstrating the biological longevity of contaminants to determine potential overlap of tissue concentrations or provide important toxicodynamic information. If available, information on the tissue dosimetry of single chemical exposures and information identifying sensitive tissues/organs and interaction with key biochemical pathways (whether related to metabolism/excretion or cellular function) should be combined to allow a more complete

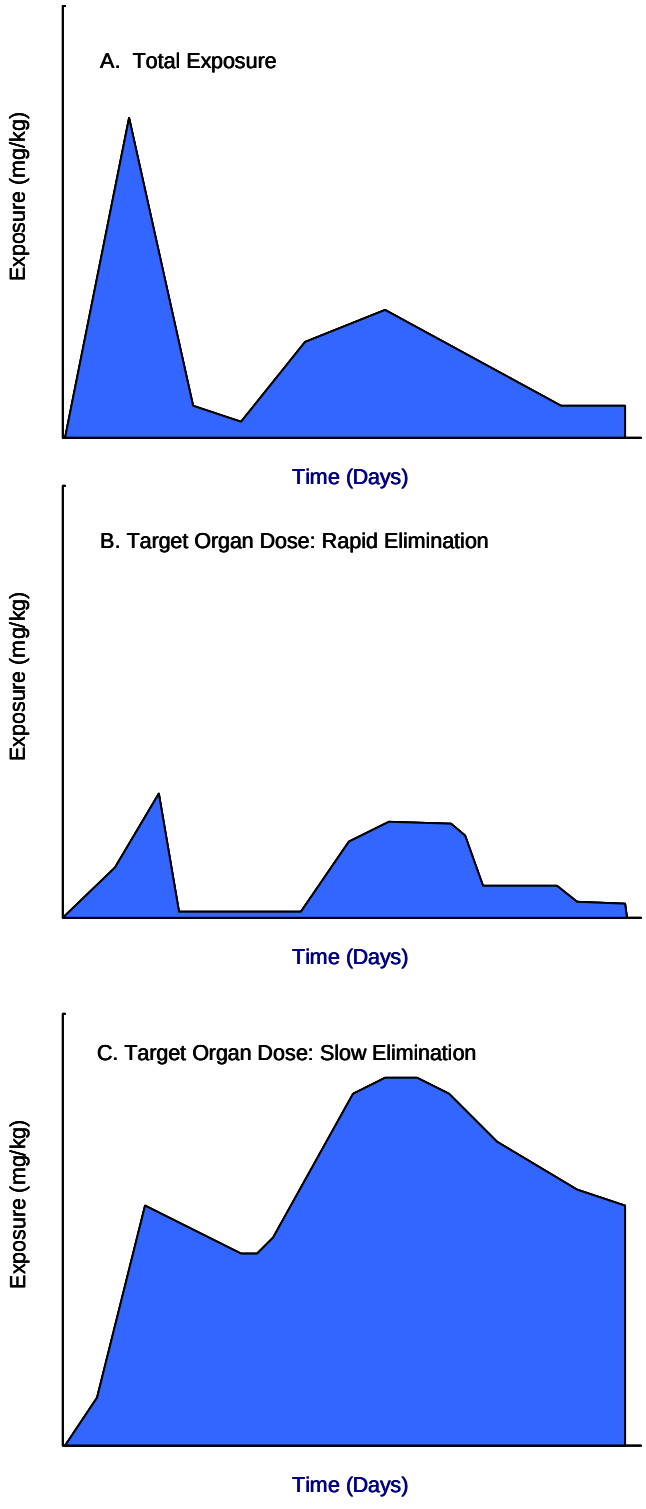


FIGURE 3-12

Multipathway Potential Doses and Target Organ Doses

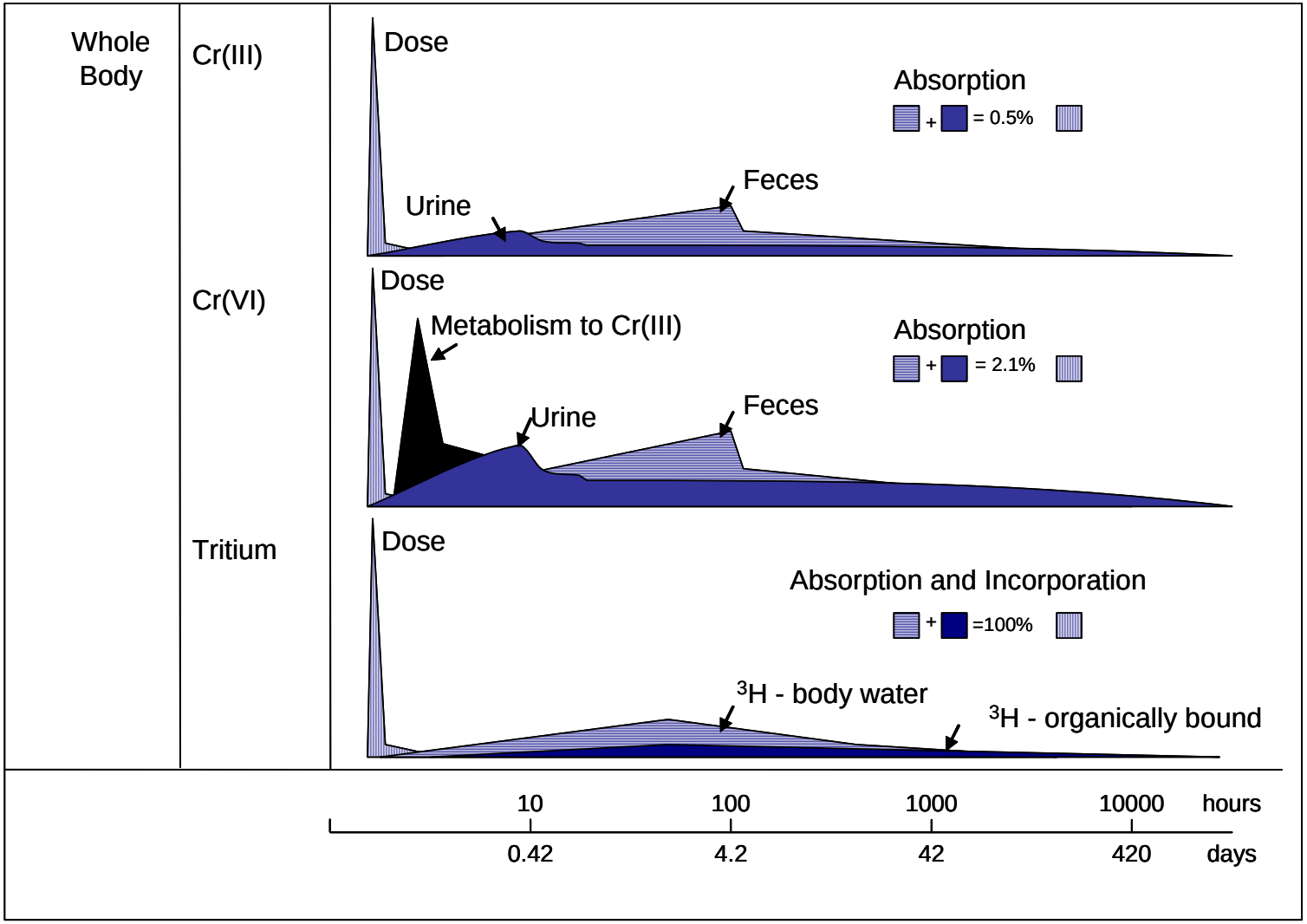


FIGURE 3-13

Human Residence Time for Selected Contaminants

evaluation of interactions among mixture components leading to changes in internal exposure duration.

As illustrated in Figure 3-14, biological effects can continue even after the chemical(s) has been eliminated from the system. Persisting biological and/or biochemical effects can have multiple effects including those based on chemical distribution and tissue effects. These effects can relate to subsequent exposures to the same chemical and to other chemicals, depending upon the extent to which multiple chemicals interact with the same biochemical or cellular targets.

Finally, even a qualitative description of the possible alteration of effects based on exposure sequence and pattern constitutes a step forward. The exposure sequence could be an issue for chemicals in different media at different times. For example, combined exposures from multiple routes could have occurred if an individual's past exposure history is considered. These current and past exposures via the same or different exposure routes/media may increase an individual's susceptibility to a chemical (U.S. EPA, 2003e). A database of chemical pairs for which exposure timing should be considered would be useful for cumulative assessments. The Agency has developed initial information in its Mixtox database, which is described in Chapter 4. Some information related to exposure is included in the interaction profiles that have been drafted by ATSDR for a limited set of chemical combinations (see Appendix A). Further discussion of toxicity as influenced by exposure sequence is presented in Chapter 4.

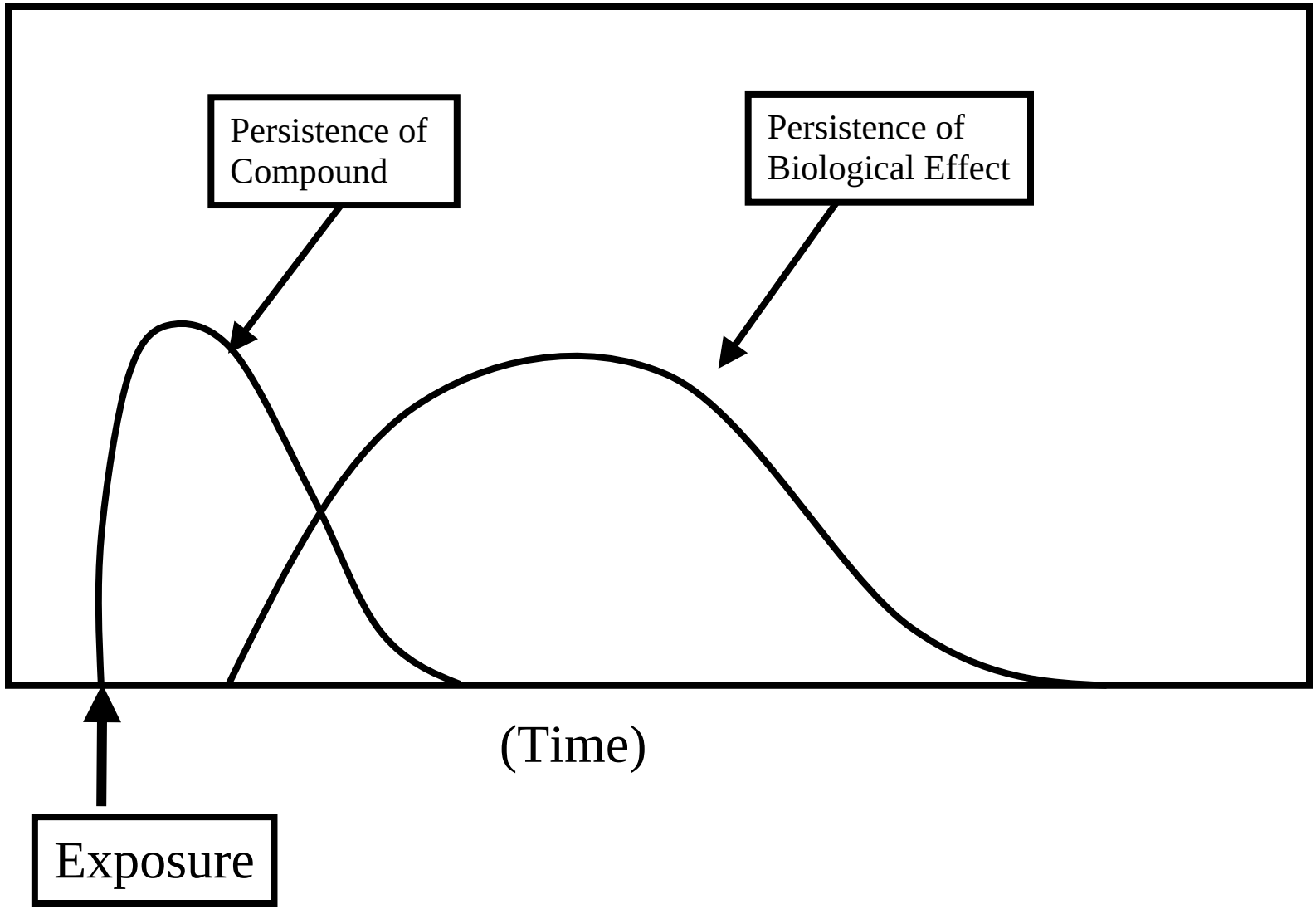


FIGURE 3-14

Conceptual Illustration Showing the Persistence of a Biological Effect Exceeds the Duration of the Exposure

3.4. ILLUSTRATION OF CUMULATIVE CONCEPTS FOR THE AIR PATHWAY AT A CONTAMINATED SITE

Local communities are understandably concerned about possible exposures to chemicals from contaminated sites, with air and groundwater being two main transport pathways. When the water table is reasonably shallow and local citizens are using nearby wells, the groundwater pathway can be a main concern under the current no-action condition. The air pathway can be an issue, for example, when the surface is still contaminated with volatile compounds, when wind speeds are high enough to carry contaminants in surface soil off-site, or when operating facilities with stacks are present.

Sites without operating facilities are not usually of concern for ambient air quality or public health under baseline conditions. However, cleanup of these sites can be a much different story. Air is considered the principal pathway by which the public could be exposed to site contaminants during the cleanup period. To emphasize the importance of evaluating risks associated with possible cleanup measures for both workers and the public, the following discussion illustrates cumulative considerations for the air pathway during the cleanup period for a contaminated site. Many of the same general concepts discussed here would also apply to the assessment of the groundwater pathway. A number of tools that may help evaluate the groundwater pathway are included in tables within Appendix A.

Several cleanup alternatives are typically evaluated for contaminated sites, ranging from no action (the baseline case) to various actions that can include excavating soil and waste, decontaminating and demolishing buildings, treating wastes, and transporting them for disposal, all of which involve airborne releases. Thus, for the cleanup period, air contamination is typically a community's major environmental

concern. The basic steps of an air pathway analysis for a cumulative assessment are summarized in Text Box 3-12. Results are ultimately used to guide emission control strategies to minimize impacts. In assessing this pathway, emission rates are estimated for site-related sources and air dispersion is modeled to predict the amounts and possible distributions of multiple contaminants at locations of interest, which typically include the site boundary and representative receptor locations such as homes or schools.

Basic Steps for Cumulative Air Analysis
(Text Box 3-12)

1. Create an emissions inventory for multiple sources
2. Model air dispersion for multiple chemicals
3. Estimate exposures for receptors (to translate to risks)

Of course, actual measurements of particulate and multiple airborne chemicals would best characterize current site conditions, however, a comprehensive air monitoring program is extremely expensive and accuracies decrease near the threshold of detectability, which is often the level of interest for environmental projects. Thus, measured data are usually limited and air quality models must be applied to assess impacts. Uncertainties related to air modeling are thought to be acceptable when considering the high cost of monitoring.

These models combine relevant meteorology data with site emission estimates to mathematically simulate atmospheric conditions and calculate where and when released contaminants will reach receptor locations, as well as where and how much particle deposition will occur. Even when some data are available, monitoring will never be able to measure concentrations for all chemicals at all locations. Therefore, modeled estimates will be needed to fill those gaps. Models can also determine impacts of one source from among many (source attribution) and forecast how concentrations will

change if a given emissions source is modified. In addition, air dispersion modeling is the only way to assess impacts from sources that do not yet exist. They are valuable tools for assessing potential impacts associated with both existing emission sources and those projected during the cleanup period. Their benefits are summarized in Text Box 3-13. Illustrative information to guide the development of emission inventories for a cumulative assessment at a contaminated site is offered in Section 3.4.1, and information to guide dispersion modeling for these sites is given in Section 3.4.2.

Benefits of Dispersion Models *(Text Box 3-13)*

Fill gaps in monitoring data to predict levels & co-locations of combined chemicals from site releases

Avoid detectability constraints, high monitoring costs

Identify contributing sources to joint concentrations

Project impacts from new facilities being considered

3.4.1. Emission Inventories. Cleanup of a contaminated site can involve many different sources of emissions. Various source configurations and examples are point (incinerator stack), area (waste impoundment or pile), volume (water treatment facility), and line (road). Some sources are stationary while others are mobile. Common emission sources at these sites are summarized in Text Box 3-14. At many sites, distinct areas of contamination can contain different combinations of chemicals at different concentrations.

Multiple Emissions during Cleanup
(Text Box 3-14)

Fugitive dust from mechanical disturbance of soil by heavy construction equipment during excavation (scaled to chemicals/concentrations at each area)

Dust emissions from construction and material/waste transportation vehicles

Contaminant emissions from on-site treatment systems (such as an incinerator or air stripper)

Windblown dust from cleared areas (when threshold wind speed is exceeded)

Emissions of volatile and semivolatile organic compounds due to soil disturbance (otherwise trapped in subsurface soil pore spaces, migrating only slowly)

Particulates and mixtures exhaust from diesel-burning, heavy construction equipment (bulldozers, front-end loaders, field generators) and transport vehicles

For cumulative assessments it is important to clearly group the chemicals at each source area so they can be appropriately scaled to the fugitive emissions estimated for

that source. This will assure that the model projects the appropriate chemicals and concentrations from that source at the receptor locations, and it will enable the combined chemicals at those receptor locations from multiple sources to be back-tracked to the originating source and activity.

Emission factors are developed for these activities, but they do not provide any information on the temporal or spatial patterns of releases nor on the greatest potential emission source, which is needed to develop effective control measures. That information is developed at the next step when emission estimates are used in the air dispersion models. To guide the development of emissions inventories for many situations including contaminated sites, the Agency has developed a number of databases and methods. The Air/Superfund series provides considerable coverage of topics and methods, including an overview of air assessments, estimation of emissions from baseline and cleanup activities, and ambient air monitoring and modeling. Specific types of emissions that would be grouped in a cumulative assessment are also discussed, such as emissions of volatile and semi-volatile compounds from disturbed soil. Key resources are highlighted in Text Box 3-15. Users of these and similar information sources should characterize whether they likely lead to an overestimate, underestimate, or central tendency estimate of the emissions from these sources.

Emission Factors for Multiple Sources

(Text Box 3-15)

Information	Resource
Emissions from point and area sources	EPA Technology Transfer Network, AP-42 *(www.epa.gov/ttn/chief/ap42/index.html)*
Methods to assess specific emissions	Air/Superfund National Technical Guidance Study Series (*www.epa.gov/ttn/amtic/files/ambient/other/airsuper/superfnd.txt)*
Estimation software	EPA ClearingHouse for Inventories and Emission Factors (CHIEF) *(www.epa.gov/ttn/chief/)*

Of special interest for cumulative assessments are exposures to chemical mixtures. Notably for site workers, engine emissions from equipment and vehicles represent such a chemical mixture since diesel exhaust is considered a chemical mixture for which some toxicity information exists (see Chapter 4). These and other mobile source emissions can be evaluated using tools developed by EPA, as summarized in Text Box 3-16. As noted for Text Box 3-15, users should characterize their confidence in emissions estimates developed from sources, such as those cited in Text Box 3-16.

Mobile Sources and Multiple Chemicals

(Text Box 3-16)

Source Type:Model	***Emissions Estimated***
On-road mobile MOBILE62: *www.epa.gov/otaq/m6.htm*	Criteria pollutants (sulfur dioxide, nitrogen oxides, carbon monoxide, PM10, PM2.5, lead); hydrocarbons; carbon dioxide; ammonia; & six toxics (benzene; methyl tertbutyl ether; 1,3-buta-diene; formaldehyde; acetaldehyde; acrolein).
Non-road mobile (vehicle/ equipment engines): NONROAD *www.epa.gov/otaq/nonrdmdl.htm*	Criteria pollutants and hydrocarbons
Mobile, toxic fractions of hydrocarbons (e.g., engine exhaust) *www.epa.gov/ttn/chief/net/1999inventory.html*	Fraction-specific emissions for speciated hydrocarbons *ftp://ftp.epa.gov/pub/EmisInventory/finalnei99ver3/criteria/documentation/nonroad/99nonroad_vol1_oct2003.pdf*

Although these tools do not consider interactions among chemicals, hydrocarbon fractionation is included. By accounting for that specific input in the exposure assessment, component toxicities can be assessed with mixtures approaches that consider relative potencies (discussed in Chapter 4).

In many cases the particulate releases will dominate and other criteria pollutants will be negligible. For that situation a screening worst-case analysis could be conducted for those other pollutants to assure that estimated maximum impacts are captured in the analysis, integrated with the other projections, and presented to decision makers and stakeholders. If this approach showed that the other pollutants likely posed little risk to

the population, then this approach would lead to an increase in the attention given to the particulates.

Both contaminated and uncontaminated particulate matter (PM) may be released during site cleanup activities. The former can be released when contaminated materials are excavated and staged in stockpiles and then treated in an on-site operation or placed for transport or disposal. Uncontaminated emissions can be associated with excavating local borrow soil (used for filling, mostly sand and gravel) and backfilling and re-grading areas that are excavated on-site, or with transporting project materials (including treatment supplies) on paved or unpaved roads.

Both types of releases are addressed in a cumulative assessment. The characteristics to consider in grouping PM and associated chemicals for these assessments are summarized in Text Box 3-17. Contaminated or not, inhaled particles can affect human health as with asthma (see Chapter 4 for the toxicity discussion). Of course the multiple chemicals such as metals or organic compounds attached to particle surfaces or incorporated into the matrix are of specific interest for their joint toxicities.

Comparison of PM Properties *(Text Box 3-17)*

Characteristic	PM10: ≤10 μm	PM2.5: ≤2.5 μm
Relative weight	Heavier	Lighter
Airborne time	Minutes to hours	Days to weeks
Travel distance in air *(depends on wind speed atmospheric stability)*	100 yards to 30 miles	Farther, to 100s of miles (~like a gas)
Movement in airway after being inhaled	Impinge on sides, wedge in narrow passages	Pass through small airways, deeper in lung
Ratio of surface area to volume, relative potential for adsorbed toxics	Lower	Higher
Associated toxicity	Generally lower	Often higher

Fugitive emissions during cleanup can be estimated by considering these three factors: (1) total mass of material handled (based on the estimated volume and density), (2) total number of activity hours (e.g., for bulldozing or scraping), and (3) total number

of vehicle miles traveled (e.g., by dump trucks). In defining the mass handled, for cumulative assessments it is important to consider what materials are being combined together so representative concentrations of those materials can be appropriately grouped and scaled to the estimated emissions. For the second factor, production rates for each equipment are taken from standard reference sources (such as the Caterpillar handbook) then combined with the mass handled (determined for the first factor) to estimate the activity hours. Examples of additional factors used to estimate the emissions inventory for fugitive dust are given in Text Box 3-18.

Example Particulate Factors *(Text Box 3-18)*

Fugitive dust emissions can be estimated using a lumped emission factor for heavy construction activities, which is given as 1.2 tons total suspended particulates (TSP) per acre per month of activity. To estimate PM10 and PM2.5 emissions, respective particle size multiplication factors of 26% and 3.8% can be applied to the TSP for unpaved roads, considering that equipment traffic over temporary roads at construction (cleanup) sites are major dust emission sources (U.S. EPA, 1995a, Chapter 4). A similar lumped or grouped approach could also be considered for emissions from contaminated areas.

Further, at many sites the contaminated source areas will be widely scattered. Thus, in estimating fugitive emissions for cumulative assessments it is useful to consider when different areas will be addressed so the emissions estimated for activities conducted in the same time period can be appropriately grouped for joint evaluation in the dispersion modeling.

To illustrate how site-specific information can be reflected in an exposure assessment, the construction plan and schedule for cleanup activities are often available in general contractor plans, as well as information on expected equipment, based on preliminary engineering estimates. These data can be used to select emission factors for those specific unit operations per construction phase (see U.S. EPA, 1995a, Chapter 4).

3.4.2. Dispersion Modeling. The Agency has developed guidelines for air quality modeling and has made many air dispersion models available within two general categories: screening and refined. (These can be obtained via the EPA Support Center for Regulatory Air Modeling *www.epa.gov/scram001*, as indicated in Appendix A.) Screening models involve relatively simple estimation techniques and generally use preset, worst-case meteorological conditions to produce conservative estimates of the air quality impact of a specific source or source category. They are used instead of more detailed (and more expensive) models to assess sources that clearly will not cause or contribute to ambient concentrations above any of the following:

- ambient standards (such as the National Ambient Air Quality Standards [NAAQS] or Prevention of Significant Deterioration (PSD) levels)
- health criteria (such as threshold limit values [TLVs] or permissible exposure limits [PELs]) developed for daily workplace exposures, or
- risk-based public health guidelines.

If results of conservative screening analyses indicate that multiple chemical concentrations from one source or a combination of sources might not meet ambient standards and health criteria, then refined models would be applied for a more representative assessment.

Refined models include methods to address physical and chemical atmospheric processes, and more detailed input data produces more site-specific estimates. These two levels of modeling are often paired, with a conservative screening approach used first to eliminate contributors that clearly do not pose a concern in the cumulative context, followed by a more refined analysis. However, for many situations the screening models are practically and technically the only viable option for estimating

impacts of multiple sources with multiple chemicals. In those cases, it is especially important to ensure that input data are sound. (These issues are discussed a bit later when specific models are discussed.) Inputs to the model are summarized in Text Box 3-19.

Air Dispersion Model Inputs *(Text Box 3-19)*

Source characteristics: Emission data scaled for multiple chemicals by source, location, type, and geometry *(for type and geometry, (1) point: stack height and diameter, stack exit temperature, and exit velocity;* (2) *area: length and width, release height, and initial vertical dimensions; (3) volume: release height, and initial lateral and vertical dimensions)*

Data for nearby buildings, to address downwash effects

Meteorological data, for both surface and upper air

Topographic information for sources and receptors

Model control options (e.g., for dust control efficiency)

Air dispersion models are not designed to address certain cleanup activities. For example, they do not directly model dispersion from specific contaminated soil excavations, as emissions can only be estimated for a select set of standard source types (point, area, volume, and line). For this reason, some simplifications and modifications are usually needed to approximate characteristics of emission sources using engineering judgment, so they can be considered generally representative of actual site conditions.

Before beginning the calculations for a cumulative assessment, emission sources should be identified and grouped into a manageable number of sources and types for the modeling effort. To illustrate, air strippers, incinerators, and *in-situ* vapor extraction units would be grouped as point sources, while lagoons or surface impoundments would be grouped as area sources, conveyor belts or material dumping would be volume sources, and mobile (vehicle) emissions along haul roads would be line sources. The geometries of these emission sources also serve as inputs to the model.

The presence of nearby buildings is also of interest for cumulative analyses, notably when addressing stack releases from existing facilities or those predicted from a

facility being considered (e.g., incinerator for site wastes). Turbulent wakes downwind of structures can affect concentrations of stack releases in the vicinity, especially when the stack height is not much taller than the building. This phenomenon, referred to as *building downwash*, generally tends to increase maximum ground-level concentrations of pollutants because it brings part of the stack effluents to the ground near the source (instead of their being carried at a height to a farther distance from the stack). Compared to when there are no buildings nearby, downwash changes the location of the maximum pollutant concentrations as well as the spatial distribution of the concentrations, in particular for near-field receptors (e.g., within several miles). Thus, estimated pollutant levels can differ considerably depending on whether the model considers nearby buildings, and this can affect estimates for nearby receptors.

Additional considerations for modeling releases of multiple chemicals from a stack and for assessing impacts of multiple sources at multiple receptor locations, are indicated in Text Box 3-20 (from U.S. EPA, 1985).

Example Model Input Considerations
(Text Box 3-20)

When the height of a stack for an existing or planned facility is lower than suggested by good engineering practice (GEP), building downwash should be considered. (The GEP stack height is 2.5x the building height for common configurations, i.e., for buildings wider than they are tall; the actual formula is the height plus 1.5x the lesser of the structure height or projected width.) To account for terrain elevation effects, elevation data for multiple emission sources and receptors are also needed.

For the air dispersion model to produce relevant results, the meteorological data inputs must represent site conditions. Some sites have meteorological towers (such as larger federal research/industrial sites), but in many cases meteorological data are taken from National Weather Service stations. To define the array of receptor points for which concentrations of released contaminants will be predicted, a receptor grid is developed for the model. These inputs are highlighted in Text Box 3-21.

Also important is the nature of the input data used to define the concentrations of multiple chemicals at the receptor locations of interest. In some studies, data from an

emissions database are used (e.g., TRI data). Because these do not represent ambient levels from which exposures can be estimated, it is useful to indicate what proportion of input data is from that database versus other information sources that are more relevant to exposure concentrations. Implications for the results should be addressed in the uncertainty discussion (see Chapter 5). Similarly, when monitoring data are used, it is helpful to indicate their relevance to exposure point concentrations, for example to identify what subset reflects ambient measurements and at what height those measurements were made, e.g., on rooftops, at ground level, or within the breathing zone (on the order of 2 m), along with some discussion of data quality.

Meteorological and Receptor Data *(Text Box 3-21)*

Meteorological data: the station selected to represent the site is based on similar spatial characteristics regarding terrain features, land use, and synoptic flow patterns. Typically, hourly surface and twice-daily upper air data are available from the National Climatic Data Center, NCDC *(www.ncdc.noaa.gov/oa/ncdc.html)*; data for 1984-1992 for selected National Weather Service stations are available from EPA's Support Center for Regulatory Air Models, SCRAM *(www.epa.gov/scram001/tt24.htm).*

Two types of receptors are assessed: discrete and gridded. Discrete receptors generally represent where people actually are (e.g., in homes or schools), or monitoring stations, or places on the site boundary or property line that could be accessed by the public. Hypothetical gridded receptors are used to identify where maximum concentrations of multiple chemicals are predicted.

A model commonly used for conservative screening analyses is the steady-state Gaussian model SCREEN3 (available at www.epa.gov/scram001/tt22.htm#screen). This model estimates 1-hour ambient concentrations from only one source (point, area, or flare), but it can address many combinations of wind speed and atmospheric stability class. Its main benefit is that it is quick and easy to use. It runs interactively on a personal computer to calculate 1-hour maximum ground-level concentrations (but not 24-hour estimates for complex terrain), as well as the distance to the maximum concentration from the single source.

In order to apply this model for multiple release points, some combine these multiple emission sources to be represented by a single theoretical point. In that case,

the basis should be justified with setting-specific information, including relative proximity to other sources and to receptors, and relative impact (insignificance) for predictions at those receptor locations. While this simplifying approach is quite appropriate when emission sources are far from potential receptors, it can lead to inaccurate results if the site is near a populated area.

A key disadvantage is that because of its conservative assumptions, it can generate quite unrealistic results, e.g., highly conservative values that expectedly would never be measured. The fact that this model for cumulative assessments cannot consider multiple sources, actual meteorological data, or averaging periods other than an hour is another disadvantage. Predicted short-term concentrations are used to assess acute effects, while long-term concentrations are used to assess chronic effects. Thus, SCREEN3 results for the 1-hour period must be manually converted to other averaging times, and contributions from multiple sources must be combined to address cumulative issues.

To illustrate how this averaging time adjustment is made, multiplication factors are given in Text Box 3-22 (from U.S. EPA, 1992b). These scaling factors are recognized as conservative and could overestimate impacts by 2 to 10 times. (The actual magnitude of the overestimation is unknown and likely depends on site and source characteristics.) When a model produces unrealistic estimates, the generalizing assumptions should be revisited and replaced with more situation-appropriate inputs (for example, releases might initially have been assumed to be ground-level rather than stack or exit height from the

Factors to Adjust 1-Hour Averages to Other Times

(Text Box 3-22)

Time	*Factor*
3 hours	0.9 (± 0.1)
8 hours	0.7 (± 0.2)
24 hours	0.4 (± 0.2)
annual	0.08 (± 0.02)

building). In this way the assessment is iterated from an overly conservative but quick and cheap screening approach to a more representative but resource-intensive approach as warranted to produce realistic results that can be used for the decisions.

Refined dispersion models are used when more detailed analyses are needed. These include steady-state Gaussian plume models such as ISC3-PRIME or AERMOD, which require relatively intensive efforts and computer resources. (They are available at www.epa.gov/scram001/tt26.htm#iscprime, www.epa.gov/ttn/scram/tt26.htm#aermod.) The main advantage of these models for cumulative assessments is that they can simultaneously evaluate a large number and different types of emission sources to estimate particulate (and scaled multiple-contaminant) levels over a wide range of averaging times, to address exposure periods from acute (e.g., for 1, 3, 8, and 24 hours) to annual time frames. Concentrations of multiple chemicals at different receptor locations can be attributed to specific sources by setting up source groups for each model run and identifying contributions from a given source within that group.

These refined models improve upon the screening models for cumulative assessments by including dry and wet deposition algorithms, thus producing estimates that can be used to assess multiple pathways (by providing deposition estimates rather than being limited to inhalation). However, they still do not account for chemical reactions because chemicals are essentially assessed one at a time and then results are combined. However, some models do account for changing concentrations for an individual chemical over time by incorporating exponential decay. A general comparison of the capabilities of screening and refined models for cumulative risk assessments is offered in Text Box 3-23.

In general, steady-state Gaussian models are not used for areas beyond 50 km (30 mi) because the steady-state assumption does not hold. For large study areas, dispersed concentrations can be estimated using models that can simulate regional-scale, long-range dispersion as well as local-scale, short-range dispersion, e.g., the non-steady-state Lagrangian puff models such as CALPUFF *(*available at www.src.com/calpuff/ calpuff1.htm*)*. For areas covering thousands of kilometers, Eulerian models such as the Community Multi-scale Air Quality (CMAQ) modeling system would be used *(*see www.epa.gov/asmdnerl/models3/*)*. This model was designed to address overall air quality considering multiple inputs, but it is very labor-and resource-intensive; the amount of computer time needed is much longer than for steady-state Gaussian models, so these models would probably not be appropriate for most site assessments. As a note, CMAQ does address chemical reactions but these are only for ozone and acid rain, not air toxics. The source code would have to be modified to add algorithms for chemical processes for the contaminants of interest at a given site to account for those potential interactions.

Model Capabilities for Cumulative Air Analyses
(Text Box 3-23)

Scope	Screening Model	Refined Model
Multiple chemicals	One at a time (individual runs)	Yes, combined, and as scaled to particulates
Multiple sources	One at a time (individual runs)	Yes, many of different types, simultaneously
Multiple pathways	No, just provides estimates for air	Yes, because also estimates deposition
Multiple time periods	No, only 1-hour averages	Yes, 1-hour to annual averages
Source attribution at receptors	No	Yes, from the grouped sources contributing to pollutants at those points
Changes over time	No	Some cover attenuation (for individual chemicals)
Chemical interactions	No	Not for metals and organics at sites (only ozone, acid rain)
Realistic predictions	No, conservative concentrations	Yes, as constrained by relevant data availability

Certain site studies might consider other point sources that could contribute to cumulative air impacts, either as assessed by the project team or in a complementary assessment. Some analyses have considered generic distances within which dispersion is to be assessed; some recent studies have indicated a distance of 20 km (12.5 mi); a generic radius of 80 km (50 mi) has historically been used in environmental impact assessments. However, this potential impact radius should be determined from setting-specific features (including meteorology, terrain, and nature of emissions) that affect the area over which airborne releases will travel. The dispersion model itself can be used to define an appropriate study distance, by identifying a target level and determining at what distance that target would be reached. This could be some fraction or percent of background (e.g., 10%) or of the initial release, considering associated health effects.

3.5. SUMMARY COMPARISON AND SCREENING SUGGESTIONS

A general comparison of the exposure assessment process conducted for basic health risk assessments and for cumulative exposure assessments is summarized in Text Box 3-24.

As this summary shows, the basic topics and outcomes are the same. The cumulative column simply highlights additional attention that would be paid to certain features in explicitly considering cumulative risk issues. Cumulative risk assessments evaluate aggregate exposures by multiple pathways, media, and routes over time, plus combined exposures to multiple contaminants from multiple sources.

Practical suggestions that can be considered in conducting the exposure assessment for cumulative health risk assessments at these sites are offered below, with an emphasis on screening for grouped evaluation.

Comparison of Exposure Assessment Processes *(Text Box 3-24)*	
Basic Assessment	Cumulative Assessment
What general question is being addressed?	
How could people be exposed to chemicals, what would the amount of exposure be?	Similar, but emphasizing combined source contaminants and cumulative exposures
What is evaluated?	
Individual Sources/releases of chemicals	Emphasis on combined sources/releases (sources may not be located in community)
Behavior of individual chemicals in the environment (transport/fate)	Emphasis on joint behavior, considering environmental interactions, differential transformation, and grouped sets of chemicals
Concentrations of chemicals at points of human contact	Emphasis on sets of chemicals that coexist initially and those that move together
People who "represent" current conditions and likely future land use	Representative receptors as for the basic case, paying attention to sensitive subgroups and unique exposure activities (e.g., per cultural practices)
Routes by which people could be exposed to each chemical	Emphasis on combined chemicals and routes over time, considering sequencing
Amount of each chemical taken in over time	Emphasis on combined amounts of various forms (potential impact on toxicokinetics)
How are results used?	
Estimated intakes are linked with toxicity information to assess potential harm	Estimated intakes are considered in groups to guide more explicit evaluation of joint toxicity to assess potential health harm

* Implementing existing guidance, which identifies many cumulative risk issues, is enhanced by more explicitly acknowledging *joint evaluations* and at least qualitatively indicating the potential for interactions to define groupings.

* An initial conservative screening of relative risks can be conducted to identify the sets of contaminant *sources, receptor locations, and pathways* to be analyzed in detail. Focus on grouping the chemicals, affected media, and exposure points that are expected to contribute to combined pathway exposures for those receptors, considering media and time frames.

* Because relatively few major sources might account for most of the hazards associated with a site, *focus first on the main sources* especially when resources are constrained. However, following that initial focus iterate through the assessment process to assure that cumulative exposure issues have been appropriately considered.

* In modeling chemical transport and fate, account for environmental *transformation over time* (including mixtures), and adapt transport/dispersion models to account for multiple chemicals, e.g., *scaling to source* concentrations for those chemicals moving together, and defining source attributions at multiple receptor locations.

* In developing groupings for chemicals and exposure pathways, focus on the potential for relatively *high exposures to sensitive populations* and possible contribution to induction of *health effects that already exist* at relatively high levels in the study population, in addition to those with high inherent hazard (toxicity) in combination with the amount present; potential interactions with other chemicals; and tendency to persist, bioaccumulate, and/or be transported between environmental media.

* To screen potential vulnerable or susceptible subgroups into the enhanced cumulative assessment process, pursue existing data such as indicator information in *demographic studies and health registries*.

* Consider the *total exposure context* to evaluate whether contributions from site contaminants combined with existing body burdens might exceed levels that are expected to be safe. For stakeholders desiring a more explicit assessment of total exposure, to cover chemicals not related to the site, indicate information resources that can be used to guide such a complementary assessment.

4. CUMULATIVE TOXICITY ASSESSMENT

This chapter provides detailed information on the cumulative toxicity assessment issues that are described in Chapter 2. The goals of Chapter 4 are to define cumulative toxicity assessment (Section 4.1), summarize existing U.S. EPA guidance for conducting toxicity assessments, including chemical mixtures risk assessments (Section 4.2), and then expand those ideas to include cumulative risk issues. These additional issues include multiple route exposures at various time frames (Section 4.7), the value of pharmacokinetic information in evaluating internal co-exposures (Section 4.3), consideration of secondary and tertiary effects (Section 4.5), and the impact of chemical interactions on cumulative risk (Section 4.6). A flow chart is presented in Section 4.4 for the purpose of facilitating and organizing the risk assessor's effort to evaluate toxicity groups for cumulative toxicity risk assessment. The goals of the approach presented in this chapter are to provide a way to group chemicals by their potential for joint toxic action as a refined classification of the cumulative exposure groups (developed in Chapter 3) and then to provide cumulative risk assessment methods for addressing multiple toxic effects, multiple exposure routes, and toxicological interactions for chemical mixtures. The result is the identification of chemical groups (and single chemicals) that should be evaluated for a particular population, including vulnerable subpopulations.

This chapter presents a number of approaches, some of which can be easily implemented with existing data and published methods and some of which would be resource intensive in terms of data collection and analysis. They are all shown here in the interest of advancing the field of cumulative risk assessment and for the purpose of

providing the Agency with readily available, scientifically sound cumulative risk assessment methods.

4.1. DEFINING CUMULATIVE TOXICITY ASSESSMENT

Toxicity assessments that support cumulative health risk assessments evaluate a population's potential to develop adverse health effects from exposures to multiple chemicals through multiple routes of exposure over time. As discussed in Chapter 2 (see Figure 2-1), cumulative risk assessment emphasizes a community focus where the population may be exposed to multiple stressors, potentially from multiple sources. Thus, information developed in the initial assessment phase regarding the population profile is important to the ensuing toxicity assessment, including considerations related to vulnerability (i.e., susceptibility/sensitivity, differential exposure, differential preparedness, and differential ability to recover). In addition, such assessments may need to consider the potential for multiple health effects to occur and for joint toxic action from multiple route exposures to chemical mixtures. Timing and intensity of exposures to different chemicals may need to be evaluated, including the evaluation of internal co-occurrence of multiple chemicals and toxicological interactions in the target tissue(s).

4.2. U.S. EPA TOXICITY ASSESSMENT GUIDANCE

The general methods the Agency uses for toxicity assessment are detailed in a number of risk assessment guidelines and guidance documents, as illustrated in Text Box 4-1. The Agency Program Offices use these various documents to conduct assessments and also to develop additional guidance and tools specific to their respective media and sites. Information regarding toxicity assessment and many other

aspects of risk assessment can be found within the U.S. EPA's Web site (www.epa.gov). For example, to supplement its primary guidance for site assessments (U.S. EPA, 1989a), Superfund provides a set of tables to be used as templates for conducting hazard index calculations (online at http://www.epa.gov/oswer/riskassessment/ragsd/tables.htm).

Most of the documents providing risk assessment guidance (see Text Box 4-1) focus on specific health endpoints such as cancer, mutagenicity, reproductive and developmental effects, and neurotoxicity. These documents can be used in a cumulative toxicity assessment to evaluate their respective health endpoints; the resulting information can then be combined using guidance that deals with cumulative risk issues such as the *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixture* (U.S. EPA, 2000a) or the *Methodology for Assessing Health Risks Associated with Multiple Pathways of Exposure to Combustor Emissions* (U.S. EPA, 1998a). Guidance also is available for evaluating toxicological mechanisms of action, including those related to cumulative risk for pesticide

Selected Information Guides for Toxicity Assessment *(Text Box 4-1)*

Risk Assessment Guidelines of 1986, including chemical mixtures, mutagenicity, cancer, exposure assessment, developmental effects (U.S. EPA, 1986, 1987)

Risk Assessment Guidance for Superfund (U.S. EPA, 1989a)

Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991)

Reproductive Toxicity Risk Assessment Guidelines (U.S. EPA, 1996a)

Guidelines for Neurotoxicity Risk Assessment (U.S. EPA, 1998b)

Guidelines for Ecological Risk Assessment (U.S. EPA, 1998c)

Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures (U.S. EPA, 2000a)

Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity (U.S. EPA, 2002c)

Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005f)

Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (U.S. EPA, 2005g)

exposures (U.S. EPA, 2002c) and for mechanisms of carcinogenicity (U.S. EPA, 2005f). The assessment of vulnerable subpopulations is also addressed by Superfund in their site assessment guidance (1989a) and specifically for children in a supplemental guidance to the 2005 carcinogen risk assessment guidelines (U.S. EPA, 2005g). In summary, there are a number of Agency resources that describe methods and approaches that can be used to address various aspects of cumulative toxicity assessments for community-based cumulative risk assessments.

4.2.1. U.S. EPA Practices for Evaluating Chemical Mixtures. The U.S. EPA evaluates risks from exposure to chemical mixtures using peer-reviewed Guidelines (U.S. EPA, 1986, 2000a) that identify both component-based and whole mixtures methods (Figure 4-1). The selection of a method (e.g., Hazard Index, Relative Potency Factors) depends on the availability of information on toxicological joint action and chemical composition of the mixture. The simplest component-based methods utilize single chemical exposure and dose response information to form a mixtures assessment and are useful in comparing mixtures containing the same chemicals but in various concentrations and proportions. Component-based methods include those based on assumptions of response addition (toxicologic independence) and dose addition (toxicologic similarity). These methods, however, do not directly address interaction effects among components (i.e., effects greater than or less than those observed under a definition of additivity). To address the latter concern, the Interaction-Based Hazard Index method may be applied, using information on binary (pairwise) interactions among chemicals in a mixture to modify its Hazard Index (see Section 4.6.2 for details on this method). The main toxicologic considerations for the component-

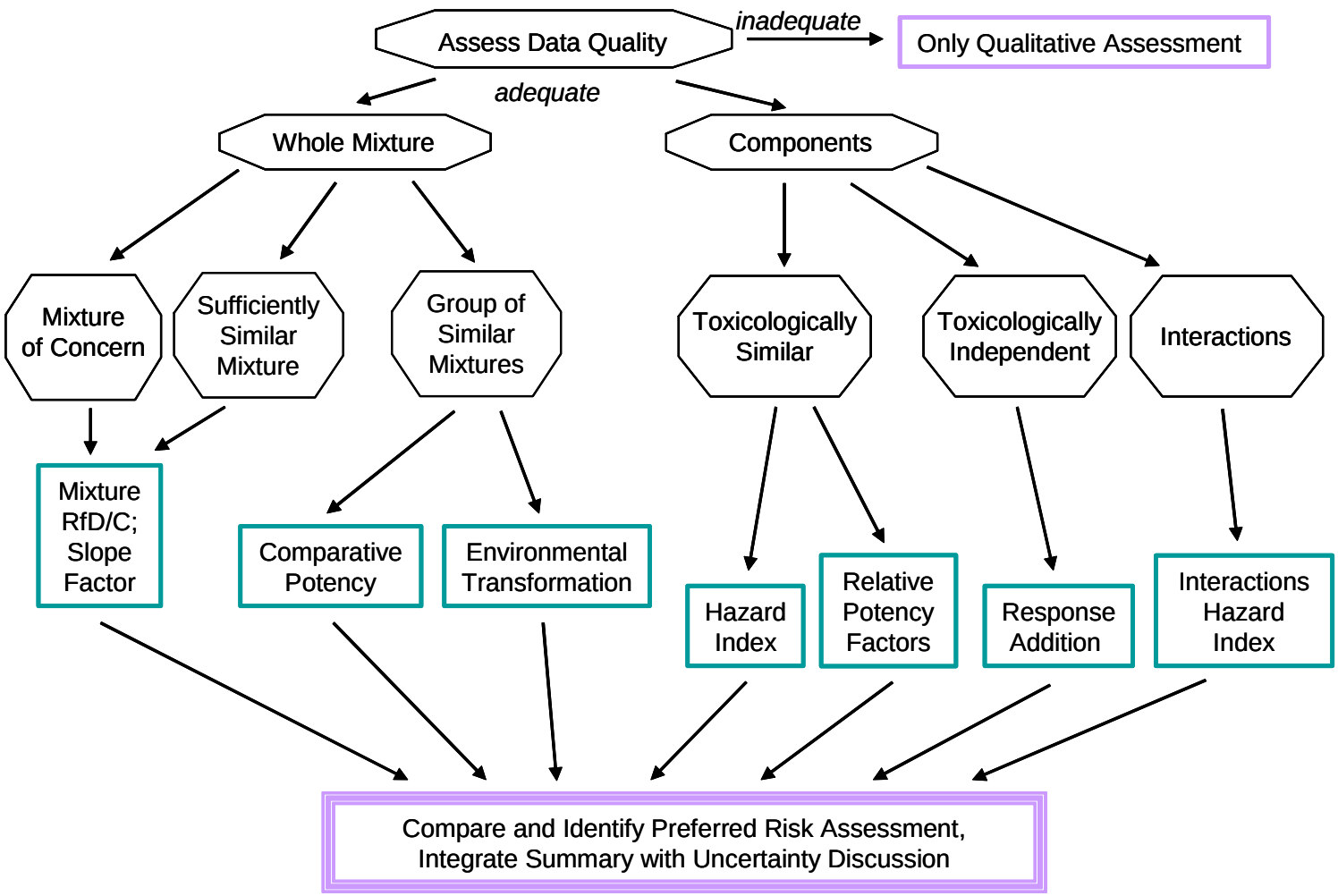


FIGURE 4-1

Approach for Assessing Mixtures Based on the Available Data (U.S. EPA, 2000a)

based risk assessment methods used by U.S. EPA are then toxicologic independence, toxicologic similarity, and pairwise interaction.

Whole mixture methods (e.g., mixtures reference doses, environmental transformations) account for unidentified chemicals in a complex mixture and inherently incorporate joint toxic action among chemicals. Dose response assessments based on tests of whole mixtures or on epidemiological data determine combined effects empirically. Examples of these (U.S. EPA, 2005c) include (1) Reference Doses on commercial PCB mixtures (Aroclors 1016 and 1254) based on primate data and (2) a cancer slope factor for coke oven emissions based on human occupational exposures. Drinking water disinfection by-products represent a complex mixture for which epidemiological data suggest potential health risks (U.S. EPA, 2003f). A U.S. EPA study, called the 4-Lab project, is currently underway to toxicologically and chemically characterize this complex mixture to produce data on reproductive and developmental effects in rats exposed to concentrations of this complex mixture for use in risk assessment (Simmons et al., 2002).

The usefulness to a cumulative risk assessment of toxicologic data on a whole mixture depends strongly on how similar the studied mixture is to the environmental mixture of concern (U.S. EPA, 2000a). The fundamental requirement for what is called "sufficient similarity" is that the complex mixture being considered as a surrogate have roughly the same major chemical components in approximately the same proportions as the environmental complex mixture to be evaluated. Any additional information on toxicologic similarity, i.e., data on similar health effects and dose-response relationships for the two complex mixtures or their common components, may also be useful in

establishing similarity. The U.S. EPA's mixtures risk guidance discusses several issues with determining toxicologic similarity of two complex mixtures. For example, either the Reference Dose (RfD) or cancer potency for a complex mixture can be determined by treating the mixture as if it were a single substance and using the dose-response data on that substance in the same fashion that single chemical dose-response data are used. The main concern is that the mixture composition (relative proportions of the component chemicals) remains fairly constant.

Cumulative risk assessments add layers of complexity to evaluation of the complex mixture. For example, oral, dermal, and inhalation exposures may occur in the same population over varying timeframes. Although a mixture risk assessment can be conducted for each route of concern, methods for incorporating multiple route exposures into a mixture evaluation are being developed. Unfortunately, multi-route exposures to a complex mixture cannot be addressed by treating the mixture as a single substance. The combination of route-specific whole mixture dose-response data for two different exposure routes is complicated because of potential interactions between the two routes for some components and because the relative contributions of some components to the mixture toxicity can be different for the two routes.

Multi-route dose-response methods seem promising with use of mixture component data. One method is to estimate internal doses using pharmacokinetic modeling for each chemical separately for each route of exposure and combine these to represent a combined internal blood or target organ tissue dose (Teuschler et al., 2004; U.S. EPA, 2003g). Providing the effect of concern is not a portal of entry effect (e.g.,

lung tumors for inhalation exposure), the combined internal dose can be used in the toxicity assessment.

For this report, component based methods based on dose addition and response addition are stressed as initial approaches for evaluating cumulative toxicity, with modifications to accommodate multiple effects, multiple routes, and toxicologic interactions. Dose addition and response addition are fundamentally different methods, based on different assumptions of the toxicity. The two additivity assumptions are briefly described in the following text. Extensive discussion of these mixture methods is given in the Agency's mixture risk assessment guidance (U.S. EPA, 2000a).

- *Dose addition* sums the doses of the components in a mixture after they have been scaled for toxic potency relative to each other. The predicted mixture toxicity is determined from this summed dose. Dose addition requires the component chemicals to be toxicologically similar, i.e., to share a common toxic mode of action (MOA). When dose addition is applied using an index chemical to estimate risk, then the mixture components are required to have similarly shaped dose-response curves for the endpoint being evaluated.

- *Response addition* first estimates the probabilistic risk of observing a toxic response for each chemical component in the mixture. Then, the component risks are summed to estimate total risk from exposure to the mixture, assuming independence of toxic action (i.e., the toxicity of one chemical in the body does not affect the toxicity of another chemical). This can be thought of as an organism receiving two (or more) independent insults to the body, so the risks are added under the statistical law of independent events.

4.2.1.1. Dose Addition — Superfund site assessments have applied dose addition in the form of a Hazard Index (HI) to evaluate sites for indications of health risk (U.S. EPA, 1989a). The HI is calculated as the sum of Hazard Quotients (HQs) for the chemical components of the mixture. (Note the HI is not dependent on using an index chemical to assess risk, so the components are not required to have similarly shaped dose-response curves.) An HQ is typically calculated as the ratio of a chemical's

exposure level to its safe or allowable level, such that values larger than 1 are of concern. For a group of *n* chemicals in a mixture and using the RfD as a safe, allowable level, the HI for oral exposure is calculated:

$$HI = \sum_{i=1}^{n} E_i / RfD_i \qquad (4\text{-}1)$$

where:

E_i = exposure level of the i^{th} chemical

RfD_i = Reference dose of the i^{th} chemical

A similar index for inhalation exposure uses the Reference Concentration (RfC) for the allowable level. The HI is usually calculated for groups of chemicals whose effects are observed in a common target organ. The HI is interpreted similarly to the HQ, i.e., the more HI exceeds 1, the greater is the concern for mixture toxicity. Note that the HI provides an indication of risk but is not an explicit risk estimate.

To estimate actual risk, a slightly different approach based on dose addition uses Relative Potency Factors (RPFs) for the dose scaling. Because the total dose of the chemicals in the mixture is of concern, the chemical components of a mixture are scaled for relative toxicity to an index chemical and summed to produce a total index chemical equivalent dose. In this method, the total index chemical equivalent dose is evaluated using the index chemical's dose response curve to estimate risk (see Section 4.7.1.2 for details). Note that the toxicity equivalence factors (TEFs), developed for dioxin assessment, are a special case of the RPF approach (U.S. EPA, 1989b).

As an expression of dose addition, the formula for HI has three important uncertainties (U.S. EPA, 2000a). These include:

1) The assumption of common MOA might not apply because only commonality of the target organ is considered.

2) The use of a safe level, such as a lower bound on the toxicity threshold, might not be an accurate measure of toxic potency. Weak toxicity data usually result in a lower safe level because of larger uncertainty factors or use of lower confidence bounds on dose.

3) The use of RfDs as safe levels may result in an overestimate of the degree of concern because the RfD is based on one critical or most sensitive effect. Thus, when a chemical causes multiple effects and needs to be included in more than one HI calculation, the general use of its RfD is problematic. A solution is to generate Target organ Toxicity Doses (TTD) (derived for each target organ of concern using RfD methodology) for use in target organ specific HI calculations (Mumtaz et al., 1997; U.S. EPA, 2000a).

Appropriate interpretation of the HI requires fairly detailed understanding of the individual chemical's dose-response curves, the nature and commonality of the toxic effects, and the quantitative relationship between the effect of concern and the critical effect.

4.2.1.2. Response Addition — Toxic effects described by the proportion of exposed animals showing toxicity are often determined for mixtures using response addition. For example, the probabilistic risk of cancer in a given dose group is typically estimated by the proportion of responders in that group. One can then estimate total cancer risk from a mixture by summing the individual cancer risks for the carcinogens in the mixture (U.S. EPA, 1989a). For a two chemical mixture, the mixture risk (R_m) is the sum of the risks for chemical 1 (r_1) and chemical 2 (r_2) minus the probability that the toxic event from exposure to chemical 1 would overlap in time with the toxic event from exposure to chemical 2, as expressed in the following equation:

$$R_m = r_1 + r_2 - (r_1 \times r_2) \quad (4\text{-}2)$$

Risks are appropriately aggregated for cancers across various target organs because the result is interpreted as the risk of any cancer, and the cancers from each chemical component are considered to be independent events in the body.

The applicability of both dose addition and response addition can be evaluated by appropriate toxicity testing that produces dose-response data for the whole mixture and its component chemicals. Any use of the additivity formulas to obtain estimates of mixture toxicity extrapolated beyond the range of actual mixture data should be accompanied by a description of the evidence supporting the additivity assumptions, i.e., commonality of toxicity for dose addition and toxicologic independence for response addition.

4.3. TOXICOLOGY OF INTERNAL CO-OCCURRENCE

This section communicates the importance of understanding tissue dosimetry of compounds, as opposed to understanding the human exposure to them in the environment. Toxicity is a function of the contact between a contaminant chemical and its biological receptor, located in target tissues. Because of the complex nature of biochemical and physicochemical factors governing chemical disposition in the body, measures of environmental contact are insufficient to completely describe internal disposition of chemicals in the human body and the temporal description of the toxic sequella, including events that may modify the internal dosimetry of subsequently encountered contaminants. At present, there is no Agency guidance on best practices of this type of activity, though several related efforts are underway.

Toxicity assessment involves understanding and mathematically describing the relationship between exposure (dose) and effect (response). This relationship may be

quantified at several levels of specificity (Figure 4-2). At its most fundamental level, the end result may only be hazard identification, the ability to link an exposure with an adverse outcome, where the data are insufficient to inform an understanding of the dose-response relationship. The next level of detail involves knowledge of the concentration encountered in the environment, or in the cases of most toxicity studies, the administered (not the internal) dose. Increasing the level of sophistication requires knowledge of the internal dose of the parent compound and is the first level at which consideration of pharmacokinetic principles must be employed. The final two levels of complexity require solid understanding of pharmacokinetic conditions and allows the internal dose to be translated first to concentrations of the parent compound in the target tissues and ultimately to concentrations of the toxicologically active chemical species (parent or metabolite) in the target tissue. This final level of specificity requires knowledge of whether the compound is toxic in its parent form or as a metabolite. Thus, doses, and specifically internal doses, may be considered at different levels of specificity, and each is useful and differentially resource-intensive.

Because of the compound-specific nature of their disposition in and elimination from the body, not every compound contained in the same contacted environmental medium will remain in the tissues of the body for the same duration. Thus, for one chemical a given exposure may result in prolonged retention and protracted tissue exposure whereas a different compound encountered in the same environmental medium may be quickly eliminated following exposure. The toxicity analysis should summarize information demonstrating the biological longevity of contaminants to determine potential overlap of tissue concentrations (Figure 4-3, also discussed from an

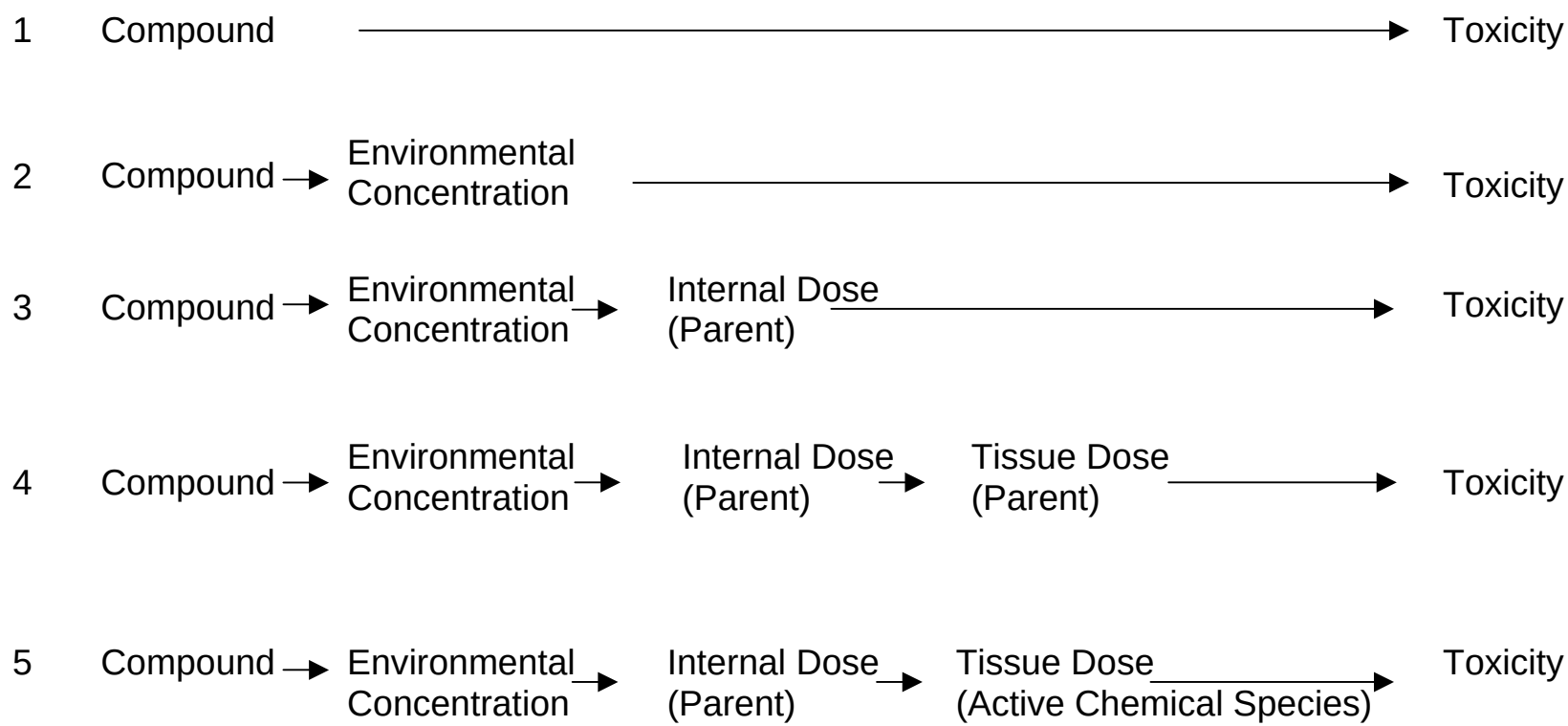


FIGURE 4-2

Level of Specificity for Dose-response Relationships

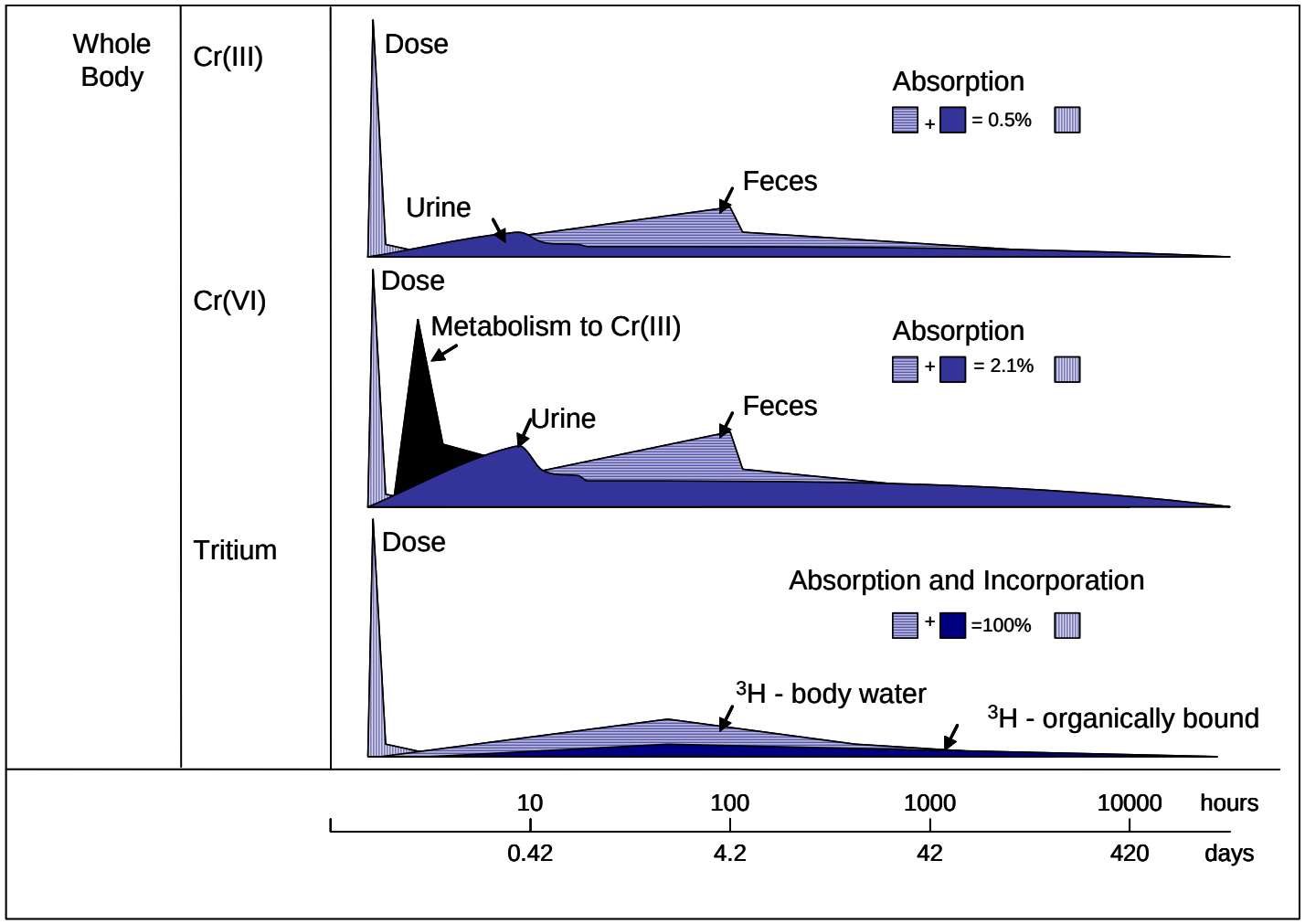


FIGURE 4-3

Human Residence Time for Selected Contaminants

exposure perspective as Figure 3-13 in Chapter 3), again focusing on doses or exposures most similar to the anticipated environmental exposure. Compounds encountered at the same time from different media and through different routes may have similar or markedly different internal exposure profiles, depending on the compound. It is important to relate either of these situations to the potential for overlapping internal dose as each defines a concurrent exposure. Information on the tissue dosimetry of single chemical exposures and information identifying sensitive tissues/organs and interaction with key biochemical machinery (whether related to metabolism/excretion or cellular function) should be combined to allow a more complete evaluation of interactions among mixture components leading to changes in internal exposure duration. Thus, there are advantages of evaluating exposures at the tissue level rather than at the level of the environmental contact.

Biological effects can continue even after the chemical is removed from the system. Persisting biological and/or biochemical effects can have multiple effects including those based on chemical distribution and tissue effects. These effects can relate to subsequent exposures to the same chemical, or other chemicals, depending upon the extent to which multiple chemicals interact with the same biochemical machinery. For example, exposure may induce, or increase the liver's content of an enzyme (Figure 4-4, also

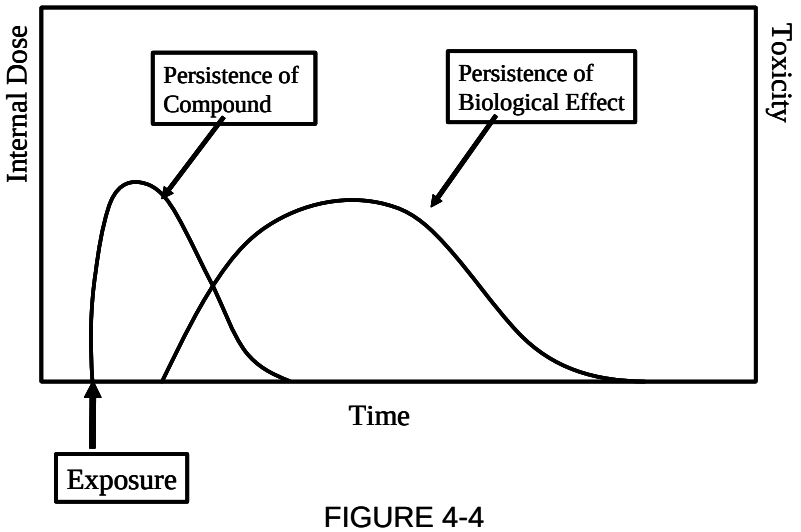


FIGURE 4-4

Conceptual Illustration of Persistence of Mixture Components

discussed from an exposure perspective as Figure 3-14 in Chapter 3). This can result in increased bioactivation and detoxication potential when that enzyme is responsible for the metabolism of additional encountered compounds (Figure 4-5). In this example (top panel), chemical A induces the expression and subsequent metabolic capacity of the enzyme responsible for metabolizing (here, hydroxylating) not only chemical A, but chemical B as well. With the increase in metabolic capacity (lower panel), increased metabolism may result in a higher toxic potential when metabolism results in a bioactivation process or lower toxic potential when metabolism represents a detoxication process. However, enzyme induction does not always increase chemical metabolism *in vivo* (Kedderis, 1997; Lipscomb, 2003, 2004). When metabolic capacity of the liver already surpasses the rate at which a chemical may be delivered to the liver via hepatic blood flow (a condition known as flow-limited metabolism), further increases in metabolic capacity, e.g., through enzyme induction, will not increase the rate or extent of chemical metabolism. The extent and duration of persistent biological effects should be determined, and its impact on the toxicity of other compounds must be investigated on a compound by compound basis.

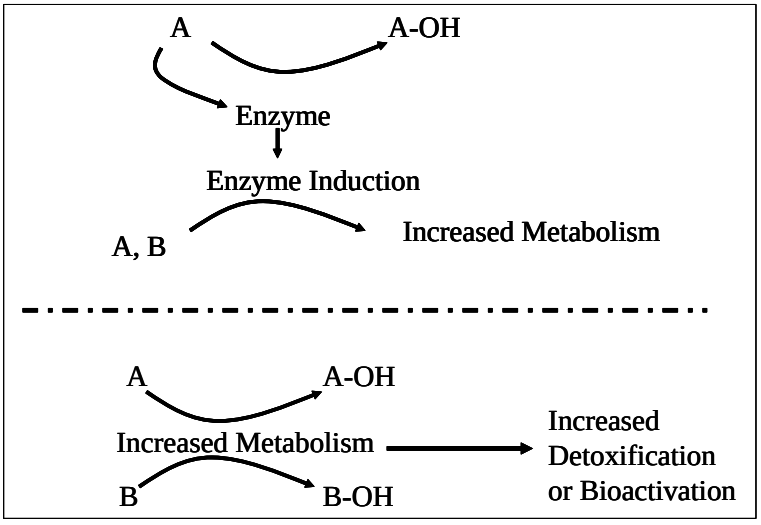


FIGURE 4-5

Conceptual Illustration of Effects of Metabolism on Toxicity

The timing of compound exposure and the duration of biological effects must be carefully considered. One well known initiation-promotion chemical interaction occurs

when the prior events associated with the toxicity of benzo[a]pyrene (DNA damage) persist beyond the chemical's residence time on the body. These effects are transformed into tumors by the subsequent exposure to a second compound, TPA (see Text Box 3-10). When the sequence of the exposure is reversed, tumors are not produced, given the short biological residence time of TPA (compared to B[a]P), and the short biological persistence of TPA's effects. Another example of the biological effects persisting beyond chemical residence time is provided by studies from Mehendale and colleagues (Mehendale, 1995; Soni et al., 1999). Their results demonstrate that low levels of tissue damage can result in stimulations of cellular repair, which are themselves protective against subsequent chemical exposure and insult occurring during the time of increased repair. Co-exposure to agents that inhibit repair capacity (e.g., chlordecone) potentiates the toxicity of the original compounds at least during the time that the biological effect (inhibition or repair) persists. This information should be summarized and considered as the toxicity assessment proceeds through the evaluation of chemical interactions.

4.4. CHEMICAL MIXTURES GROUPING AND TOXICITY ASSESSMENT SCHEME

The object of grouping chemicals for toxicity assessment is to take advantage of established chemical mixtures risk assessment approaches that rely on groups made up of individual chemicals that act through a common toxic mode of action or, conversely, are toxicologically independent of one another (while sharing a common toxic endpoint). In cumulative risk assessment, the initial four exposure categories group chemicals by exposures in the same or different media and at the same or different point in time (see Section 3.5.2.2). In this chapter, we begin with those rough

exposure groupings and further evaluate them to form revised groups based on toxicological similarity. A systematic approach is suggested to evaluate these groups using cumulative risk assessment methods.

Grouping chemicals by the potential for co-occurrence and joint toxic action is a key simplifying concept for the conduct of cumulative risk assessments. Chemical components of mixtures can be screened for inclusion in a cumulative risk assessment using the elements of component-based methods. Figures 4-6a, 4-6b, and 4-6c outline a three-step process for classifying chemicals into groups suitable for analysis and then applying the methods shown in Figure 4-1. These three steps are:

1) Figure 4-6a (same as Text Box 3-9) – Classify all chemicals of concern into initial groups by their potential to occur in the same or different media and at the same or different time. (See Chapter 3 for details on exposure assessment; Section 3.3.2.2 for information on exposure grouping.)

2) Figure 4-6b – Divide these exposure/time groups further into subgroups in which chemicals are thought to cause toxicity by the same mode of action or affect the same target organ. Include all target organs or effects for which positive evidence exists of adverse health effects. An initial step here is to collect toxicologic and pharmacokinetic data on each of the individual chemicals to be considered in the risk assessment. Factors to consider in forming these toxicity groups include pharmacokinetic parameters, persistence of the chemicals in the body, and the formation of metabolites.

3) Figure 4-6c – Assess the toxic potential of the chemicals/whole mixtures of concern using methods in Figure 4-1 from U.S. EPA Guidance (U.S. EPA, 2000a). A flow chart is shown to apply component based or whole mixture risk methods to the groups formed in Steps 1 and 2.

4.4.1. Chemical Groupings by Common Effects. The groupings developed in the exposure analysis (Figure 4-6a) categorize multiple chemicals into groups comprised roughly of exposures in the same or different media at the same or different exposure

Chemical Groupings by Co-occurrence in Media/Time		
	Media	
Time	Same	Different
Same	Group 1	Group 3
Different	Group 2	Group 4

FIGURE 4-6a

Chemical Grouping by Co-occurrence in Media and Time

	Exposure Groups			
Because of Exposure Group	Same Media; Same Time	Same Media; Different Time	Different Media; Same Time	Different Media; Different Time
Consider These Factors to Form Toxicity Groups	Similar effects or metabolites	Similar effects or metabolites; Body burden; Persistence of effects	Similar effects or metabolites; Pharmacokinetics; Multi-route exposures	Similar effects or metabolites; Body burden, Pharmacokinetics; Persistence of effects; Multi-route exposures
Target Organ Specific Toxicity Groups				
Kidney	Group 1,1	Group 2,1	Group 3,1	Group 4,1
Liver	Group 1,2	Group 2,2	Group 3,2	Group 4,2
.	***.***	***.***	***.***	***.***
.	***.***	***.***	***.***	***.***
.	***.***	***.***	***.***	***.***
Lung	Group 1,n	Group 2,n	Group 3,n	Group 4,n

FIGURE 4-6b

Chemical Groupings by Common Target Organs and Effects. Each exposure group is subdivided based on commonality or overlap of toxic effects, metabolic pathways, or tissue concentrations. Chemicals must be retained for assessment if information exists on their toxicologic interactions.

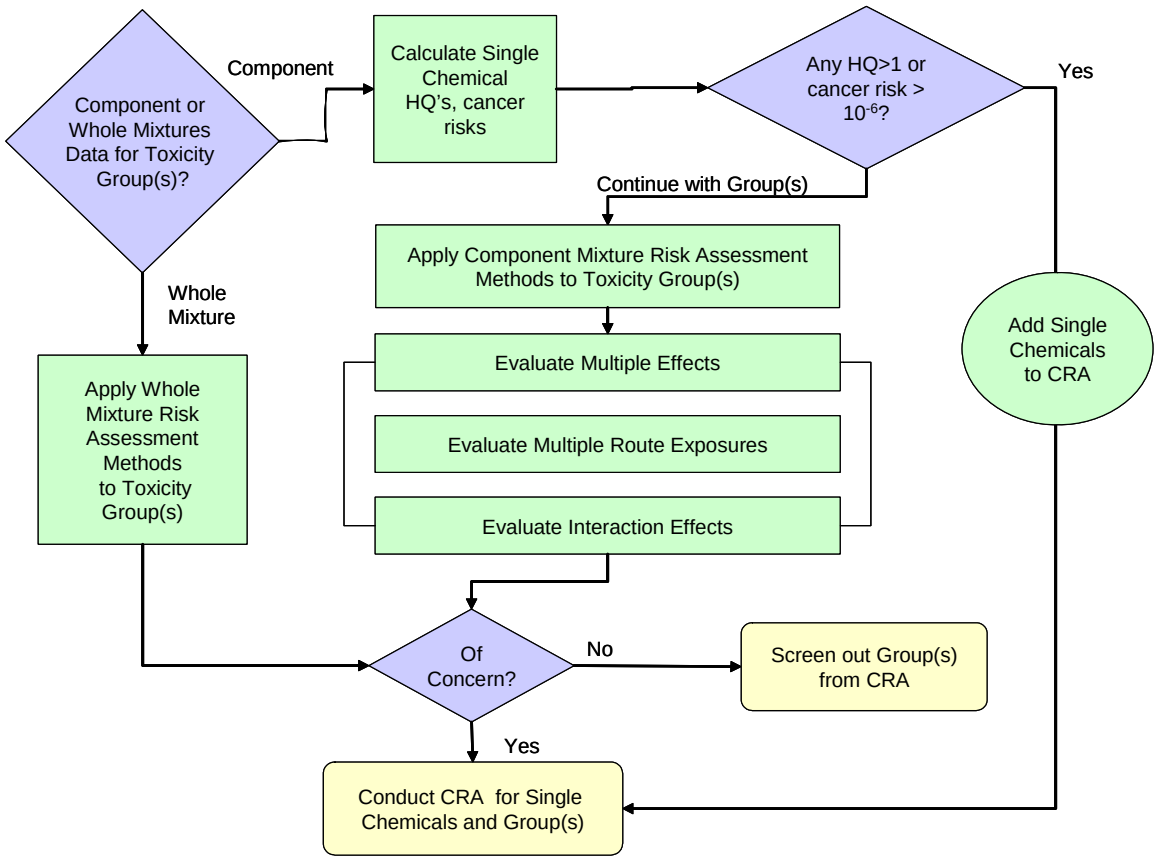


FIGURE 4-6c

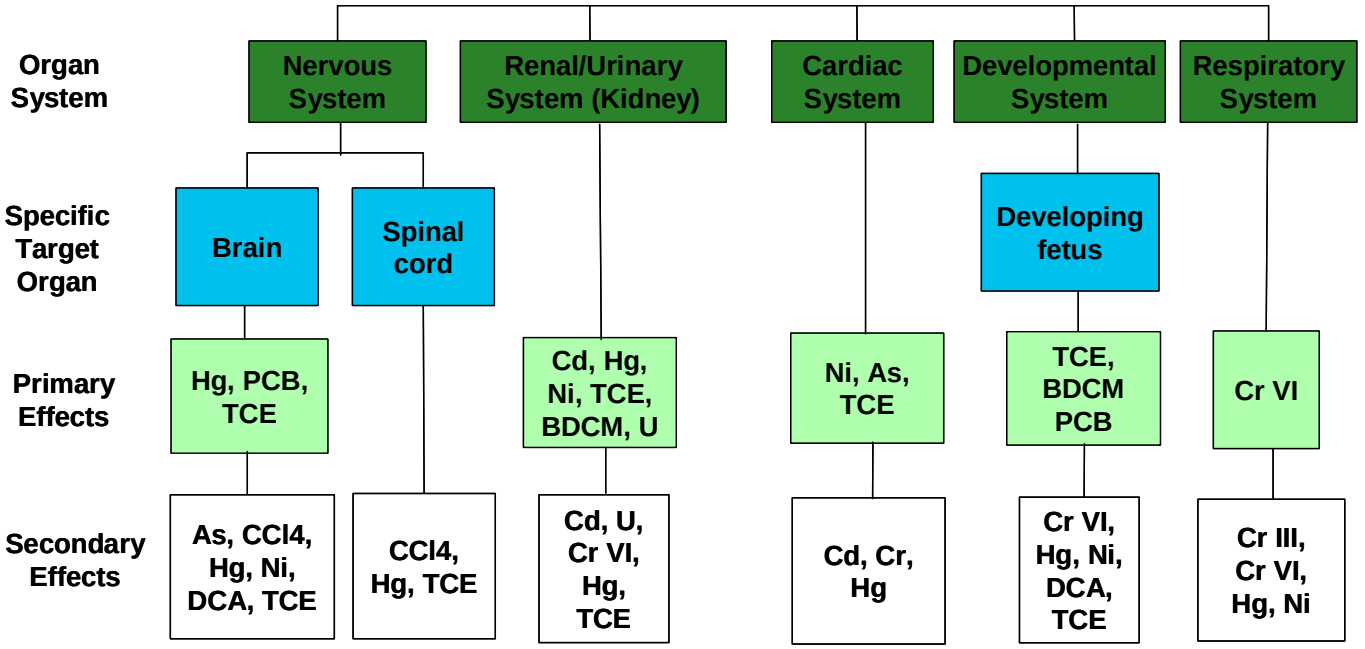
Grouping Chemicals for Cumulative Risk Assessment. The mixture risk methods are applied to each group, with "concern" judged by the appropriate screening value (e.g., mixture RfD for whole mixture oral exposure). Groups can be screened out only if both whole mixture and component methods indicate no concern.

time (see Section 3.3.2.2.). Note that many exposure groups could be formed when multiple exposure media and timeframes are found to be important to the assessment. Figure 4-6b shows that for each media/time combination, the occurring chemicals are grouped by common target organ or effect, which does not necessarily imply common toxic mechanism or mode of action. Because the exposure scenarios vary with media and time, factors relating to exposure routes and fate within the body are then considered to further refine the subgroups for the toxicity assessment (see Figure 4-6b). Through consultations among exposure analysts and toxicity analysts, several different groupings can be developed based on available exposure and toxicity data. In addition, most chemicals are likely to end up in several different groups because they can exist in more than a single medium, and they cause more than one toxic effect in different target organs. (Text Box 4-2 discusses the availability of Agency toxicity information beyond IRIS values for use in the cumulative toxicity assessment.)

Target Organ Toxicity Doses
(Text Box 4-2)

The Agency's IRIS database generally derives an oral RfD or an inhalation RfC based on a single critical effect for a single chemical. Thus, cumulative toxicity assessments using secondary effects require the development of additional dose response information beyond readily available Agency values. U.S. EPA (2000a) suggests the development of Target Organ Toxicity Doses (TTDs) for use in these situations. TTDs are developed for secondary effects using the same methodology as applied in the derivation of an RfD (Mumtaz et al., 1997). TTDs can then be used in Hazard Index calculations instead of using an RfD to represent a safe level for all target organs. The alternative is to use the IRIS RfD regardless of target organ, resulting in a likely overestimation of the HI. To date, there is not an analogous Agency alternative value for an RfC.

An example of the grouping process can be seen using the information shown in Figures 4-7 and 4-8. In Figure 4-7, several organ systems are represented (i.e., the nervous, renal, cardiac, developmental, respiratory systems), with specific target organs indicated in the second row. The third and fourth rows list chemicals causing primary or secondary effects in those systems, respectively (see Tables B-1 and B-3 of Appendix



Sources:

- **Municipal Waste Combustor: Hg, Cd**
- **Fish Consumption: Hg, PCB**
- **Drinking Water Disinfection By-Products (DBPs): BDCM, DCA**
- **Source Water Contaminants: TCE, Ni, As, CCl4, Cr**
- **Contaminated Groundwater: U**
- **Temporary Combustor for Site Remediation: Cd, Cr, Ni**

As = Arsenic (inorganic)
BDCM = Bromodichloromethane
Cd = Cadmium
CCl4 = Carbon tetrachloride
Cr III = Chromium III (insoluble salts)
Cr VI = Chromium VI
DCA = Dichloroacetic Acid
Hg = Mercury (based on mercuric chloride)
Ni = Nickel (soluble salts)
PCB = Polychlorinated Biphenyls (Arochlor 1016)
TCE = Trichloroethylene
U = Uranium (soluble salts)

FIGURE 4-7

Information on Primary and Secondary Effects Linked with Hypothetical Exposure Sources to Show Example Chemical Groups
(see Appendix B, Tables B-1 and B-3 for chemical information)

	Exposure Groups			
Exposure Group:	Same Media; Same Time	Same Media; Different Time:	Different Media; Same Time	Different Media; Different Time
Exposure Scenarios	**Air:** Daily Exposure to Municipal Waste Combustor Emissions **Air:** Daily Inhalation Exposure to Disinfection By-Products via Showering	**Drinking Water:** Acute Accidental Exposure to Source Water Contaminants **Drinking Water**: Exposure to Uranium Contaminated Ground Water, Years Later	**Drinking Water:** Daily Exposure to Disinfection By-Products via Ingestion and Showering **Fish:** Daily Exposures via Local Fish Consumption	**Air**: Short Term Exposure to Emissions from Temporary Combustor **Drinking Water:** Acute Accidental Exposure to Source Water Contaminants, Months Later
Target Organ Specific Toxicity Groups				
Kidney	Hg, Cd, BDCM	Ni, TCE, U, Cr	Hg, BDCM	Cd, Ni, TCE, Cr
Brain	Hg, DCA	TCE, As, Ni, CCl4	Hg, DCA, PCB	TCE, As, Ni, CCl4
Fetus	Hg, BDCM, DCA	TCE, Ni, Cr	Hg, BDCM, DCA, PCB	TCE, Ni, Cr
Heart	Hg, Cd	TCE, Ni, As, Cr	Hg	Cd, TCE, Ni, As,Cr
Lung	Hg	Ni, Cr	Hg	Ni, Cr

FIGURE 4-8

Example Chemical Groupings for Toxicity Assessment

B for chemical toxicity information). A primary effect is the adverse effect observed at the lowest dose on the dose-response relationship developed for each adverse effect noted from single chemical exposures. Secondary effects can be thought of in several ways, as effects mediated by chemical metabolites, as effects that follow from chemical insult but do not result in adversity (i.e., enzyme induction), or as adverse effects that occur at doses higher than those producing the critical effect. Following these rows is a list of six hypothetical exposure sources under consideration for a cumulative risk assessment and a list of the associated contaminants to which the population is exposed. This information is then used to form initial toxicity groups in Figure 4-8, which begins by setting up hypothetical exposure scenarios for each combination of same/different media and same/different time. The target organ specific toxicity groups in Figure 4-8 are developed by distributing the chemicals associated with the hypothetical exposure sources (Figure 4-7) into the five bottom rows that designate specific target organs, according to the combinations of these sources shown in the media/time exposure scenarios. In this way, contaminants that are expected to co-occur in media and time are grouped by common target organ for analysis. For example, in the first column, the population is exposed via inhalation to municipal waste combustion emissions and drinking water disinfection by-products (DBP) through showering, so the chemicals associated with these two sources are grouped by common target organ.

4.4.2. Refinement of Toxicity Groups. Once these initial groups are formed, then several other factors need to be accounted for before the groups are subjected to a risk assessment procedure. At this point, the chemicals within each group do not

necessarily act by the same toxic mechanism or mode of action and have not been considered yet in terms of whether the exposure levels are within ranges that may cause toxicity, additive joint toxic action, or toxicological interactions. These groups must be refined using considerations of appropriate exposure routes, timing of exposures and effects, persistence of chemicals within the body, and the potential for joint toxic action. This refinement results in final chemical groupings that are ready for analysis using chemical mixture risk assessment methods. The following issues should be considered:

- Are the chemicals in the toxicity groups appropriate, given the exposure routes and health effects of concern?

  Example: For the Same Media/Same Time exposure scenario, DCA is a non-volatile DBP that would not volatilize, but would be found in aerosol (water particles) during showering. Because of the relatively low level of exposure via inhaled aerosols during showering, it could be removed from the toxicity groups. Also, BDCM is known to cause renal effects via inhalation, but the toxicity data on fetal loss are from oral exposures, with no developmental data available for inhalation exposures; thus, because of the potential for a large inhalation exposure to BDCM during showering and because fetal loss is a severe effect, it would be reasonable to retain BDCM in the "fetus" grouping, but this uncertainty must be discussed in the risk characterization.

- Do data exist on toxicological interactions between chemicals in the groups that would raise concerns for increased (or decreased) toxicity from the joint exposure?

  Example: Data exist that show a synergistic interaction effect in the brain for joint exposures to TCE and CCl_4 (ATSDR, 2003a). This relationship is only documented for this one toxic effect. It is reasonable, however, to keep both chemicals listed within all toxicity groups when the exposure scenario indicates they will co-occur. Thus, in Figure 4-8, both TCE and CCl_4 would be added to all toxicity groups under exposure scenarios involving the contaminated ground water source.

- Are there metabolites that should be added to the groups and, if so, should the parent compound be retained or removed?

Example: Although this exposure scenario is not shown in Figure 4-8, suppose a same media/same time scenario involves co-exposures to the DBP, DCA, and the source water contaminant, TCE. Because DCA is a metabolite of TCE in the body and both chemicals are known to cause effects in the brain, exposures to both chemicals could result in elevated levels of DCA for consideration in the risk assessment. If the risk analyst cannot determine whether TCE would still be present or completely metabolized. It may be reasonable to also retain TCE in the risk assessment, but this uncertainty must be noted in the risk characterization discussion.

- When the population is exposed to sources at different times, do the chemicals from the first exposure remain in the body long enough to be of concern when the second exposure occurs?

Example: The potential for toxic interactions of cadmium and TCE on the cardiovascular system may be based on direct interactions in the heart itself, and by additional, indirect, effects of cadmium and TCE on kidney function related to blood pressure regulation. Both TCE and cadmium are readily absorbed into the body. TCE is eliminated from the body with a half-life measured in hours, whereas cadmium is eliminated from the body with a half-life measured in decades; thus an earlier exposure to cadmium may result in persistent body burdens, and internal co-exposure with TCE in tissues. The tissue concentrations and the effects of cadmium in the heart and kidney may persist beyond the initial exposure period, making these organs more susceptible to the injury produced by TCE.

- When the population is exposed to sources at different times, do the health effects resulting from the first exposure last long enough to be of concern when the second effect from the subsequent exposure occurs?

Example: As shown in Text Box 3-10, benzo[a]pyrene (BaP) and tris(2-ethylhexyl) phosphate (TPA) are an initiator/promoter pair. TPA does not have a tumorigenic effect in mouse skin assays, but when it is applied after initiation with BaP tumorigenic activity is greatly enhanced (Verma et al., 1985).

Figure 4-9 illustrates a few of the changes (not comprehensive) that would be made in Figure 4-8 based on the points raised in this section. Considerations of body burden, pharmacokinetics, exposure route, persistence of effects, metabolites, and multi-route exposures may be used to alter and refine the toxicity groups. When the groups are finalized then the risk assessor can move forward to conducting the cumulative toxicity assessment.

	Exposure Groups			
Exposure Group	Same Media; Same Time	Same Media; Different Time:	Different Media; Same Time	Different Media; Different Time
Exposure Scenarios	**Air:** Daily Exposure to Municipal Waste Combustor Emissions **Air:** Daily Inhalation Exposure to Disinfection By-Products via Showering	**Drinking Water:** Acute Accidental Exposure to Source Water Contaminants **Drinking Water**: Exposure to Uranium Contaminated Ground Water, Years Later	**Drinking Water:** Daily Exposure to Disinfection By-Products via Ingestion and Showering **Fish:** Daily Exposures via Local Fish Consumption	**Air**: Short Term Exposure to Emissions from Temporary Combustor **Drinking Water:** Acute Accidental Exposure to Source Water Contaminants, Months Later
Target Organ Specific Toxicity Groups				
Kidney	Hg, Cd, BDCM	Ni, TCE, U, Cr, CCl4**	Hg, BDCM	Cd, Ni, TCE, Cr, CCl_4**
Brain	Hg*	TCE, As, Ni, CCl_4, DCA***	Hg, DCA, PCB	TCE, As, Ni, CCl4, DCA***
Fetus	Hg, BDCM*	TCE, Ni, Cr, CCl_4**, DCA***	Hg, BDCM, DCA, PCB	TCE, Ni, Cr, CCl_4**, DCA***
Heart	Hg, Cd	TCE, Ni, As, Cr, CCl_4**	Hg	Cd, TCE, Ni, As,Cr, CCl_4**
Lung	Hg	Ni, Cr	Hg	Ni, Cr

*DCA removed because it is not a volatile compound; inhalation exposures are not a concern.
**CCl_4 added to account for potential interaction effects between CCl_4 and TCE.
***DCA added as a metabolite of TCE.

FIGURE 4-9

Examples of Toxicity Group Refinements

4.4.3. Cumulative Toxicity Assessment Scheme. After the joint exposure and target organ groups are determined, the toxicity assessment for each group follows the schematic shown in Figure 4-6c. This flow chart begins in the same way as Figure 4-1, the chemical mixtures guidance flow chart, in that the risk analyst examines the available data for toxicity information on the whole mixture and on the mixture components. For the toxicity groups in Figure 4-8, it is not likely that toxicity data would be available for those specific chemical combinations, so the risk analyst would follow the flow chart in the direction of component data. If data are available for each of the single chemicals in a toxicity group, then the single chemical hazard quotients and, if applicable, cancer risks are calculated. If calculations show any HQ >1 or cancer risk $>10^{-6}$, then that single chemical is designated to remain in the cumulative toxicity assessment, and it is not removed from the toxicity group. The next step is to apply the chemical mixture risk assessment methods (flow chart in Figure 4-1) to each toxicity group, using the hazard index (Section 4.2.1), response addition (Section 4.2.1) or RPF (Section 4.7.1.2) approaches as appropriate, according to the judgments made regarding toxicologic similarity of the component chemicals (see U.S. EPA, 2000a, for details on applying these methods). Finally, additional quantitative methods may be undertaken to evaluate multiple effects (Section 4.5), toxicologic interactions (Section 4.6) and multiple route exposures (Section 4.7). If quantitative data are not available to conduct the analysis, but qualitative toxicity information exists, then some discussion of these issues may be possible. If none of these mixtures assessments raises concern for population health risks, then the toxicity group may be screened out of the cumulative toxicity assessment. Otherwise, the risk analyst retains both the toxicity

group(s) and the single chemicals with elevated HQs or cancer risks and finalizes the risk assessment, including a complete risk characterization (Chapter 5).

When data on the toxicity group as a whole mixture are available, the risk assessment can use that information to estimate health risks for the toxicity group. Also, within the toxicity group, there may be a complex mixture with a chemical composition that is not fully characterized (e.g., complex disinfection by-product mixtures typically contain ~50% of unidentified total organic halide material). Toxicity may be estimated for the whole mixture (see procedure in Text Box 4-3) and compared with environmental exposure levels. For example, a Reference Dose can be calculated for the whole mixture (RfD_m) as shown for the general case and compared to the IRIS value for Araclor 1016 in Figure 4-10. The Arachlor 1016 RfD_m represents that particular PCB mixture and could be used in the cumulative toxicity assessment as a surrogate value for the PCB exposure via fish consumption with the relevant toxicity groups for effects in the brain and fetus. Returning to Figure 4-6c, if the whole mixture toxicity is shown to be of concern, then it needs to remain in the cumulative toxicity assessment.

Procedure for Estimating Whole Mixture Toxicity Values *(Text Box 4-3)*

1) **Collect and Evaluate Data**
   - Epidemiology/human data preferred, supporting toxicology data
2) **Evaluate Stability within a Mixture**
   - Variability in components and their relative proportions
3) **Assess Sufficient Similarity Across Mixtures (if applicable)**
   - Similarity across mixtures' components and relative proportions
   - Similar toxicity of two mixtures or of common components
   - Common sources or produced by similar process
4) **Conduct Dose-Response Assessment**
   - Use same procedures as for single chemicals (e.g., RfD, slope factors)
5) **Characterize Uncertainties**
   - Relevance of health effects data to environmental exposures
   - Stability of the mixture and environmental fate

(U.S. EPA, 2000a).

Complex Mixture Reference Dose (RfD_m)

General Case (U.S. EPA, 2000c)

$$RfD_m = \frac{NOAEL,\ LOAEL\ or\ BMDL}{UF_m}$$

where:

NOAEL/LOAEL = No/Lowest-Observed-Adverse-Effect Level
BMDL = Lower 95% confidence limit on an X% Effective Dose (e.g., ED_{10})
UF_m = Uncertainty Factors for the mixture (e.g., interspecies, intraspecies, exposure duration, NOAEL to LOAEL, data base deficiencies)

NOAEL, LOAEL or BMDL from experimental toxicity data on the complex mixture dose-response. Uncertainty factors are derived using expert judgment, as is the case for single chemicals. The uncertainty characterization should include the relevance of the experimental mixture from which the RfD_m is derived to the chemical composition of environmental mixtures.

Aroclor 1016 (U.S. EPA, 2005c)

$$7E-5 = \frac{NOAEL = 0.007\ mg/kg/d}{UF_m = 100}$$

where:

NOAEL = Reduced birth weight in monkey reproductive study
UF_m = 3 for rhesus monkey to human extrapolation
3 for infants as a sensitive subpopulation
3 for subchronic to chronic exposure duration
3 for missing 2 generation repro & adult male repro studies
(i.e., 100 = 3 x 3 x 3 x 3, rounded up)

Confidence in RfD is medium when PCB mixtures in the environment do not match the pattern of congeners found in Aroclor 1016; high if the environrmental mixture is Aroclor 1016.

FIGURE 4-10

Complex Mixture Reference Dose

4.4.4. Evaluating Subpopulations. Information on vulnerable subpopulations should be collected and included in the cumulative risk assessment when such information is available. An extensive treatment of how to incorporate such a risk assessment into the cumulative toxicity assessment will not be undertaken in this report, but should be the subject of future research. The Agricultural Health Study and other literature on mixture exposures and potential susceptibilities related to environmental exposures (see Chapter 1) will be useful for identifying vulnerable subpopulations of concern when conducting a cumulative risk assessment. In the development of chemical groups for evaluation at a site, the characteristics of the potentially exposed population should be evaluated (Chapter 2). Chemical mixture risk estimates for vulnerable subpopulations should be calculated separately from risk assessments on the general population and presented in a separate section of the risk characterization.

4.5. EVALUATING MULTIPLE EFFECTS

The hazard identification phase of a cumulative risk assessment must be broadened to include factors beyond those considered for single chemicals. An important difference between cumulative risk assessment and traditional single-chemical assessments is the number of health effects evaluated. The method described in Figures 4-6a, 4-6b and 4-6c shows that the cumulative risk assessment needs to include an evaluation of all adverse effects, as evidenced by available health effects data (e.g., toxicology data, epidemiology studies, human clinical trials). These effects may occur at doses or exposures higher than those causing the critical effect. Furthermore, health effects data from toxicologic studies of chemical mixtures may reveal a different set of effects, potentially in target organs other than those observed in

toxicology studies of the mixture's components individually. Finally, the set of identified effects must take into account the potential routes of exposure.

The application of the toxicity assessment to actual site exposures will often require extrapolation beyond the range of the toxicity data. If external exposure levels are used in the risk assessment, then inferences about multiple effects could be highly uncertain. When data are available and resources permit a more extensive investigation, considerations should be given to using internal chemical doses based on pharmacokinetic and mechanistic information. For example, multiple organ systems and functions, such as the endocrine system and immune function, require specific attention since tissue dosimetry among the multiple organs/tissues components may differ among themselves and with respect to chemical components of the mixture. In such cases, a doubling of external exposure levels will not result in a doubling of the corresponding tissue doses. Chemicals that affect organs or tissues that are parts of a larger biological system should be considered as affecting the same target system. In this way, the assessment of multiple effects can be simplified by grouping the effects.

4.5.1. A Quantitative Method for Evaluating Multiple Effects. One of the goals in a cumulative toxicity assessment is to account for the joint impact of all of the major health impacts from exposure to multiple stressors. The approach demonstrated in this report involves a three step process: a dose-response model for multiple effects, hazard calculations using both dose-addition (Hazard Index) and response-addition approaches, and a comparison of the results. This approach would begin by analyzing dose response relationships for each single chemical, incorporating all toxic effects in the same modeling procedure. Various statistical models could be applied (e.g.,

multivariate normal linear regression, ordinal categorical regression) to predict the probability of observing an array of toxic effects for a given dose. For many chemicals, the available data on multiple effects differ across effects as well as across chemicals in terms of completeness, range of doses covered, and level of detail, making multivariate approaches difficult. In this report a simpler categorical regression model based on toxicologic judgment will be used to illustrate estimating the probability of a certain level of (non-specific) response, given exposure to a single chemical. From the modeling results, a risk estimate for the exposure of interest can be made, and a benchmark dose (BMD) can be estimated (e.g., a 5% effective dose or ED_{05}). To apply response addition, the individual chemical risk estimates must be summed across chemicals to calculate the mixture risk. To apply dose addition, an HI will be calculated using the single chemical BMD estimates to provide an indication of risk for the mixture. These results can then be compared in the risk characterization step (see Chapter 5) to evaluate the potential health impacts for the site of interest.

Ordinal categorical regression is a statistical modeling procedure that allows for a dose-response assessment of several toxicologic effects at once. The use of a categorical regression procedure to express the risk of adverse health effects for toxicological data was first proposed by Hertzberg and Miller (1985) and Hertzberg (1989) and then demonstrated with several chemicals (Guth et al., 1991; Farland and Dourson, 1992; Rao et al., 1993; Dourson et al., 1997; Teuschler et al., 1999; Strickland and Guth, 2002).

In this procedure, toxicity data, regardless of the type of effect, are interpreted using toxicological judgment in terms of pathological staging. Toxic effects, which may

include both quantal and continuous data, are classified into ordered categories of total toxic severity (e.g., categories 1-4 refer to none, mild, moderately adverse, and severe effects, respectively). The model reflects a regression of dose on the category of effect, yielding the probability that a given dose will result in a level or category of response (e.g., the probability of observing a level 3 adverse effect, given dose). The U.S. EPA software, CATREG, is useful for conducting this procedure (U.S. EPA, 2000c,d). In addition, CATREG has the ability to incorporate other factors in the analysis, including duration, study effects, species, and censored data (Guth, 1996; Guth et al., 1991, 1997). Thus, models may be developed to describe dose-risk relationships for a variety of exposure scenarios.

In Teuschler et al. (1999), categorical regression analysis was used to model the relationship between the logarithm of human equivalent doses and category of cholinesterase inhibition for each of five pesticides. Table 4-1 shows an example using three ordered categories of toxic severity for cholinesterase data (Dourson et al., 1997). The toxic response (or its absence) was related to the explanatory variables, dose and duration, by using a cumulative logistic function, and *P* was defined as the probability of observing a response of a certain severity or *a lessor response*. The logistic function used to express the relationship between *P* and the explanatory variables is given below:

$$P_i(S \le i) = \frac{exp(\alpha_i + \beta_1 x_1 + \beta_2 x_2)}{1 - exp(\alpha_i + \beta_1 x_1 + \beta_2 x_2)} \qquad (4\text{-}3)$$

where:

P_i = the probability of observing an effect of severity i or less,
S = the severity of the effect,
i = the severity category 1, 2, or 3,

TABLE 4-1

Example Severity Assignments for Cholinesterase Inhibition Data*

Severity Grade	Site	Effect
Frank Effects	Cholinergic effects	Severe abdominal pain, nausea and/or vomiting, diarrhea
	Cholinergic effects	Seizures, severe disorientation or confusion, excitation
	Whole Body	Mortality
Adverse Effects	Brain, whole blood or red blood cell (RBC) acetylcholinesterase	Inhibition (e.g., of 20% or greater)
	Cholinergic effects	Mild: Muscular weakness or twitching
	Cholinergic effects	Mild: Blurred vision and/or watery eyes, pinpoint pupils, excess salivation, sweating or clamminess
	Nervous system	Hyperactivity or altered patterns of locomotion
Non-Adverse Effects	Plasma, whole blood or RBC acetylcholinesterase	Inhibition (e.g., observed, but less than 20%)
No Effects	All	No effect

*Adapted from Dourson et al. (1997)

α_i = an unknown intercept parameter associated with severity i,
β_1 = an unknown slope parameter associated with the dose,
x_1 = the dose of the chemical,
β_2 = an unknown slope parameter associated with the duration of exposure,
x_2 = the duration of the exposure to the chemical.

Using Equation 4-3 with such data, the dose-response relationship for multiple effects can be given as the probabilities of toxic effects for a given duration and dose (e.g., the probability of an adverse effect for a 1-day exposure at 0.1 mg/kg/day), and BMDL estimates can be determined (e.g., lower bound on the dose causing a 5% chance of a non-adverse effect). Results of the categorical regression equation can then be used in response addition and the HI to present a range of potential health risk for the exposure of interest. In particular, using Equation 4-1 (from Section 4.2.1) for the HI, the RfD for each chemical can be replaced by the BMDL for multiple effects divided by an uncertainty factor (e.g., UF=100) to account for inter- and intra- species differences. The equation would then be:

$$HI(effects) = \sum_{i=1}^{n} \left(\frac{E_i}{BMDL_i / UF_i} \right) \quad (4\text{-}4)$$

A probabilistic mixtures risk estimate could also be calculated for multiple effects using the categorical regression results. Based on Equation 4-2, for ordered severity categories of 1 = no effects, 2 = not adverse effects, 3 = adverse effects, 4 = frank effects), response addition under categorical regression for a specific exposure of interest is calculated:

$$R_m(effects) = 1 - \prod_{i=1}^{n} P_i(severity \leq 2) \quad (4\text{-}5)$$

4.5.2. Interpretation. These two methods for dose-response assessment of multiple health effects yield very different types of answers. The HI(effects) is expressed as a risk indicator and the Rm(effects) is expressed as a probabilistic risk estimate. A group of chemicals should be screened in as part of a cumulative risk assessment when either the value of an HI is greater than or equal to some pre-determined level (e.g., 0.5) or a response addition risk estimate is greater than or equal to an acceptable risk level (e.g., 1×10^{-6}). In either case, when estimates approach or exceed these "cut off" values, toxicologic judgment is needed to evaluate the chemicals and data used in the analysis and to determine the level of concern for the analysis. For a cumulative risk assessment screening exercise, if either "cut off" value is met or exceeded, then those chemicals should be kept in the cumulative risk assessment. The factors considered when evaluating dose and response addition in mixture risk assessments also apply here but only in a rough sense: whether the collection of effects seem to be toxicologically similar across the set of chemicals or seems to be independent, particularly at the exposure levels under consideration. As described in the U.S. EPA (2000a) mixture guidance, these formulas give similar results when component exposures are low.

4.6. EVALUATING INTERACTION EFFECTS

Toxicologic interactions are defined in U.S. EPA (2000a) as any toxic responses that are greater than or less than what is observed under an assumption of *additivity*. The term *additivity* is used when the effect of the combination of chemicals can be estimated directly from the sum of the scaled exposure levels (dose addition) or of the responses (response addition) of the individual components. Many terms are used to

represent various kinds of interaction effects (e.g., inhibition, antagonism, masking). The most common and general of these refer to effects that are greater than additive (i.e., synergistic) or less than additive (i.e., antagonistic).

The detection of interaction effects varies from toxicologic judgment to statistical determinations. For cumulative risk assessment, interactions information should be collected from the toxicologic and epidemiologic literature and used to inform the grouping process. U.S. EPA has two collections of bibliographic summaries of interaction studies that are available to the public: the Integral Search System (Arcos et al., 1988) and the MIXTOX database (Marnicio et al., 1991). ATSDR has also published a number of interaction profiles for common environmental contaminants (Pohl et al., 2003). For example, in Table 4-2, the non-additive interactions are shown for four metals: arsenic, cadmium, chromium, and lead (ATSDR, 2004). As Table 4-2 shows, even when interactions data exist, the situation is complicated because the direction of interaction can be different for different effects or for changes in the sequence of exposure. For metals, toxicologic interactions are more troublesome because environmental conditions (e.g., pH) can alter the speciation and bioavailability of the metals. At a minimum, when evidence of synergistic interaction is found for two or more chemicals within a group (formed using Figure 4-6b) those chemicals should be included in the cumulative risk assessment. A further quantitative evaluation may be conducted using the interaction-based HI (see Section 4.6.2 and Chapter 5).

4.6.1. Toxicology of Interactions. A mixture can consist of chemicals that cause a unique toxicologic expression that was not anticipated from the toxicity of the individual compounds; the toxicodynamic process of one compound influences that of another

TABLE 4-2

Joint Toxicity: Non-additive Effects of Metal Pairs on Systems/Organs Using Oral Exposure

Effect of Metal↓ on Metal→	Not Additive*	Arsenic	Cadmium	Chromium	Lead
Arsenic	Higher				Neurological
	Lower		Blood Kidney Male reproductive	Kidney	Blood Kidney
Cadmium	Higher				Neurological Male reproductive
	Lower	Blood			Blood Kidney
Chromium	Higher	Skin			
	Lower	Kidney			
Lead	Higher	Neurological	Male reproductive		
	Lower	Kidney Blood			

* Higher = Effects are greater than expected under additivity
Lower = Effects are less than expected under additivity
Source: ATSDR (2004)

(e.g., one compound causes toxicity and a second compound slows the process of cellular repair). The toxicity of chemical mixtures is dependent upon the interactions of mixture components at either toxicokinetic (TK) or toxicodynamic (TD) processes, thus, interactions at either level may result in mixtures interactions. TK processes govern tissue distribution of compounds and include both passive and active processes. Toxicodynamics includes the effects or events that are dependent upon the contact between the toxic chemical species and the biomolecules responsible for the effect. Interactions at the TK level occur when tissue dosimetry is altered due to gross tissue alteration or chemicals interact at the same metabolic enzyme.

In addition to separating interactions according to TK or TD, toxicologic interaction among compounds may be direct or indirect. Examples of direct interaction include those demonstrated by compounds altering the same biochemical pathway or cell type or organ/tissue that is directly related to the toxic effect of the compound. Examples of indirect interaction include chemicals that may alter the internal dosimetry/metabolism of other compounds (e.g., enzyme induction, glutathione depletion) and thus exert an indirect effect on their toxicity. Examples of direct interaction include competition for key metabolizing enzymes, receptor binding sites and lipid peroxidation leading to membrane damage and radical formation. Some of these interactions will depend on the severity of the effect produced. If the effect of the first compound only results in a slight functional decrement and is recovered quickly or is compensated by the tissue, then such an effect, whether direct or indirect, may not be sufficient to serve as the basis for an assumption of interaction. Knowledge that a given effect may be reversible or compensated for by the cell must be coupled with

information on the dose-response and temporal characterization of the reversibility. This applies also to cellular/biochemical systems which are redundant and may be directly or indirectly related to toxic effects (e.g., at what point glutathione depletions lead to susceptibility).

Information on acute toxicity should be evaluated carefully. The manifestation of acute toxicity (toxicity evident in close temporal proximity to the exposure) generally requires chemical exposure levels that are greater than those required to produce delayed effects. Further, doses sufficient to produce acute toxicity bring a higher likelihood that fundamental biochemistry can be perturbed to produce TK and/or TD interactions among compounds. Interactions observed with acute toxicity, however, are generally poor indicators of interaction at lower exposure levels. Tumor production is a multi-step process, and interactions may be several, ranging from the classic initiation-promotion type interaction, to adduct formation and inhibition or repair capacity. For compounds thought to interact in the tumorigenic process, a rich data set is required to substantiate an interaction. However, when compounds are tumorigenic, regardless of the mechanism, placing them in the same group is warranted. For compounds with a tumorigenic mode of action defined to the point that a non-linear, or threshold-like, dose-response relationship can be defended, the severity of the underlying effect (e.g., cytotoxicity and cellular regeneration) must be considered. For compounds that must be metabolized to be tumorigenic, TK interactions at the enzyme level are an important aspect and should be evaluated.

4.6.2. A Quantitative Method for Evaluating Interaction Effects. To account for chemical interactions in a site assessment, the U.S. EPA recommends applying the

Interaction-based Hazard Index (HI_{INT}) to component data (U.S. EPA, 2000a). The main assumption for the HI_{INT} is that interactions in a mixture can be adequately represented as departures from dose addition (Hertzberg et al., 1999). The method follows an obvious approach: begin with the dose-additive HI (Equation 4-1) and then modify its calculation to reflect the interaction results, using plausible assumptions to fill in the data gaps. Because toxicologic interactions have been mostly studied with binary mixtures, the HI_{INT} includes information only on binary interactions; an assumption is then that higher order interactions are relatively minor compared to binary interactions. Noting that the first summation shown is the additive HI and the second summation shown is the modification for interactions, the formula for the HI_{INT} is:

$$HI_{INT} = \sum_{j=1}^{n} HQ_j \sum_{k \neq j}^{n} f_{jk} M^{B_{jk} g_{jk}} \qquad (4\text{-}6)$$

where:

HI_{INT} = HI modified by binary interactions data,

HQ_j = hazard quotient for chemical j (unitless, e.g., daily intake/RfD),

f_{jk} = toxic hazard of the k^{th} chemical relative to the total hazard from all chemicals potentially interacting with chemical j (thus k cannot equal j). To calculate, the formula is:

$$f_{jk} = \frac{HQ_k}{\left[\sum_{j-1}^{n} HQ_j\right] - HQ_j} \qquad (4\text{-}7)$$

M_{jk} = interaction magnitude, the influence of chemical k on the toxicity of chemical j. To calculate, estimate from binary data or use default value = 5

B_{jk} = score for the weight of evidence that chemical k will influence the toxicity of chemical j (see U.S. EPA 2000a for numerical scores).

g_{jk} = degree to which chemicals k and j are present in equitoxic amounts. To calculate, the formula is:

$$g_{jk} = \frac{\sqrt{HQ_j * HQ_k}}{\left(HQ_j + HQ_k\right)/2} \quad (4\text{-}8)$$

The current weight-of-evidence (WOE) classification and scores are given in Table 4-3 (U.S. EPA, 2000a). This scheme does not focus specifically on the types of data available to support a WOE determination but on the interpretation of the data made by an analyst or a group of analysts. The binary WOE factor B_{jk} reflects the strength of evidence that chemical k will influence the toxicity of chemical j, and that the influence will be relevant to human health risk assessment. In general, the more extrapolation required, the weaker the evidence is. For example, if the available interaction data were from *in vitro* studies with effect measures not directly related to the toxicity of concern, or represented a different exposure route or duration, then the WOE score would be low. ATSDR has a similar but more structured scoring rule. The factor need not be the same for the influence of chemical j on the toxicity of chemical k; i.e., $B_{jk} \neq B_{kj}$. The weight-of-evidence determination begins with a classification of the available information, followed by a conversion of that classification into a numerical weight.

This formula assumes a constant magnitude of interaction (M=5) and a limited influence of mixture composition (i.e., dose ratio of the two chemicals). Both these properties are likely to depend on the actual component exposure level and effect under consideration. The toxicology assessment is then more useful to the risk characterization if the evidence for toxicologic interactions can be discussed in the context of the likely exposure ranges and array of effects of concern.

1

TABLE 4-3

Default Weighting Factors for the Modified Weight of Evidence

Category	Description	Direction	
		Greater than Additive	Less than Additive
I	The interaction has been shown to be relevant to human health effects and the direction of the interaction is unequivocal.	1.0	-1.0
II	The direction of the interaction has been demonstrated *in vivo* in an appropriate animal model, and the relevance to potential human health effects is likely.	0.75	-0.5
III	An interaction in a particular direction is plausible, but the evidence supporting the interaction and its relevance to human health effects is weak.	0.50	0.0
IV	The assumption of additivity has been demonstrated or must be accepted.	0.0	0.0

2

4.7. EVALUATING MULTIPLE ROUTE EXPOSURES

A cumulative risk assessment should consider exposure to the population from multiple routes and pathways. Measures or estimates of internal doses may provide an improved basis both for estimating risks posed by chemical mixtures that occur through multiple exposure routes. To date, regulatory risk methods have only been published for simpler and more common approaches that use external exposure levels.

Assessments of multiple route exposures can be complicated because of a lack of toxicity data for all exposure routes of interest. If data on only one route are available, then the risk analyst must decide if it is appropriate to conduct a route to route extrapolation of the data. Such extrapolations can be problematic because of biological differences among routes in toxic responses or pharmacokinetic processes. The 2005 cancer guidelines recommend route-to-route extrapolations only on a case-by-case basis as supported by available data. There seems to be general agreement in the literature that the most appropriate way to extrapolate across routes is to employ a physiologically based pharmacokinetic model. However, both qualitative assessments and application of simple quantitative methods of route extrapolation are used as needed when data are lacking. Text Box 4-4

Agency Uses of Route To Route Extrapolations U.S. EPA (2003h) Workshop Report on Inhalation Risk Assessment *(Text Box 4-4)*

Office of Solid Waste: only does such extrapolations when there are findings that indicate it is appropriate. When it is performed, the approach is similar to that used to aggregate exposures.

Office of Air Quality Planning and Standards: treats cancer and non-cancer extrapolations differently. For cancer, in lieu of an inhalation unit risk (IUR) from the hierarchy of sources, an IUR may be derived from an oral value (using a rough breathing rate/body weight calculation), with recognition of added uncertainty. No such rough extrapolation is done to create RfCs. Because the Clean Air Act list of hazardous air pollutants is heavily weighted by respiratory toxicants, such rough non-cancer route extrapolations are generally not performed because of the high probability of missing target toxicity.

Office of Pesticide Programs: performs route-to-route extrapolations with no distinction between cancer and non-cancer endpoints. Absorption via the inhalation route (in mg/kg/day) is considered to be equal to oral absorption. Air concentration estimates for human exposure are converted from a concentration (mg/m^3) to an average daily dose expressed as mg/kg/day so that exposure can be compared directly to oral NOAEL and LOAEL values.

describes the uses of route to route extrapolation by several program offices, as presented in a 2003 U.S. EPA workshop report on inhalation risk assessment (U.S. EPA, 2003h).

4.7.1. Quantitative Approaches to Evaluating Multiple Route Exposures to Mixtures

4.7.1.1. Summing Across Routes and Pathways — EPA's Risk Assessment Guidance for Superfund (1989a) instructs risk assessors to sum HQs (Equation 4-1) and cancer risks (Equation 4-2) across exposure routes and exposure pathways, providing there is evidence of combined exposure pathways to identifiable individuals or groups of individuals who would consistently face a reasonable maximal exposure. U.S. EPA (1999b) guidance on preparing Records of Decision for Superfund site assessments provides further information on this method. (See details of this procedure in Section 5.2.1.) Although there is no discussion of summing across exposure routes and pathways in the U.S. EPA (1986, 2000a) health risk assessment guidance documents for mixtures, U.S. EPA (1989a, 1999b) establishes this approach as a policy with the purpose of accounting for any reasonable risk from multiple route and pathway exposures. U.S. EPA (1999b) provides a template for these calculations in the form of pre-formatted tables and also shows examples on its Web site (e.g., http://www.epa.gov/oswer/riskassessment/ragsd/tara.htm). For the purpose of this report, one recommended approach to account for multiple route exposures is to apply these procedures to the target organ groups developed in Figure 4-9. Further discussion of this approach is given in Section 5.2.1 in terms of a Cumulative Hazard Index, along with guidance on its interpretation.

4.7.1.2. Summing of Route-Specific Relative Potency Factors — A second approach is to estimate risks for each group and exposure route using an RPF mixtures risk assessment approach (U.S. EPA, 2000a) and then sum the risks to yield a total risk for that group by all routes. The RPF approach is a general methodology for applying dose addition to mixtures of chemicals that produce toxicity by the same MOA. Text Box 4-5 shows the mathematical formulas used to develop RPF-based risk estimates, and Figure 4-11 illustrates the process followed. To summarize the procedure, doses of mixture components are scaled by their potency relative to a well-studied component of the chemical mixture (referred to as the index chemical) using scaling factors called RPFs. The product of each mixture component's dose and its RPF is considered to be its equivalent dose in units of the index chemical. These dose equivalents of all the mixture components are summed to express the total mixture dose in terms of an Index

RPF Formulas for Risk Estimation of a Two Chemical Mixture *(Text Box 4-5)*

$$h_{mix}(d_1,d_2) = f_1(d_1 + RPF_2 * d_2)$$

where:

$h_{mix}(d_1,d_2)$ = mixture hazard or risk from joint exposure to doses d_1 of chemical 1 and d_2 of chemical 2 (dose units not specified, must be consistent for all chemicals)

$f_1(*)$ = dose-response function of the index chemical for the response(s) common to chemical 1 and the other chemicals

RPF_2 = potency of chemical 2 relative to that of chemical 1

Let pot_i be the potency estimate for chemical i. Then

$RPF_2 = pot_2 / pot_1$

For cancer risk, pot_i is often given by the slope factor of risk per unit of dose. Note that if the inverse of the effective dose (e.g., 1/ED10) is used for the potency, then RPF is the chemical 1 to chemical 2 ratio of the ED values:

$RPF_2 = ED10_1/ED10_2$

This mixture hazard formula uses the mixture dose given as the equivalent dose of the index chemical. Let ICED be the index chemical equivalent dose based on relative potency estimates (dose units consistent with d_1 and d_2). Then,

$ICED = d_1 + (RPF_2 * d_2)$

and the mixture hazard formula is

$h_{mix}(d_1,d_2) = f_1(ICED)$

Example: With dioxins, the index chemical is 2,3,7,8-TCDD. For the mixture assessment, the combined doses of all the dioxins are converted into the equivalent dose of 2,3,7,8-TCDD, and the mixture risk is then determined from the dose-response data for 2,3,7,8-TCDD.

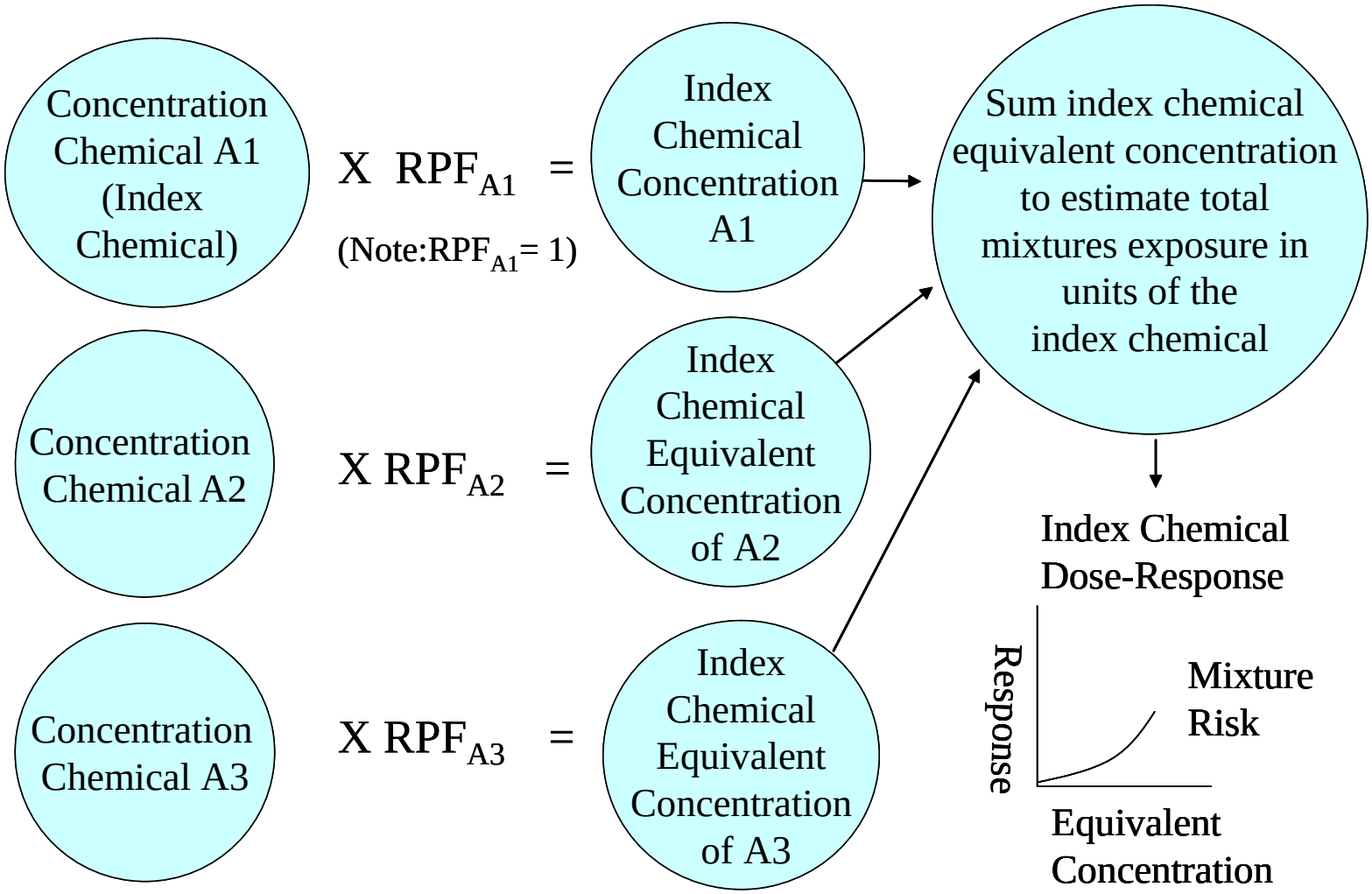


FIGURE 4-11

Schematic for Relative Potency Factor Approach

Chemical Equivalent Dose (ICED).[1] The risk posed by the mixture is then quantified by comparing the mixture's ICED to the dose-response assessment of the index chemical. To implement this approach, the index chemical must have an adequate toxicologic dose-response data set. U.S. EPA (2000a) characterized the RPF methodology as a generalized form of the toxicity equivalence factor (TEF) methodology that has been used to assess risks. This approach is similar to the Toxicity Equivalents (TEQ) method used for dioxins (U.S. EPA, 1989b) but requires a less strict interpretation of the toxicity data. Thus, it is applicable to a larger group of chemical classes than the TEQ method.

Figure 4-12 illustrates the proposed approach that combines the principles of dose addition and response addition into one method to assess mixtures risk for multiple route exposures within a group (e.g., as defined using Figure 4-9). (Using two exposure routes, inhalation and oral, Figure 4-12 illustrates how the approach estimates risk from exposure to the mixture.) Within a target organ group, an index chemical (a mixture component with high quality dose-response data that acts (or is judged to act) through the same MOA as the other members of the group for the route of concern) is selected, and ICED is calculated using the RPF approach (U.S. EPA, 2000a). (Note the text here will only refer to an ICED. However, for clarity in Figure 4-12, the ICED refers to the oral route of exposure, and the ICEC (Index Chemical Equivalent Concentration) refers to the inhalation route of exposure.) The ICED is an important concept, employed at two levels:

[1] The ICED has the same mathematical interpretation as the dioxin toxicity equivalents (TEQ). TEQ refers to the quantification of dioxin concentrations based on the congeners' equivalent 2,3,7,8-TCDD toxicity (U.S. EPA, 1989b). ICED is applied to mixtures other than dioxins.

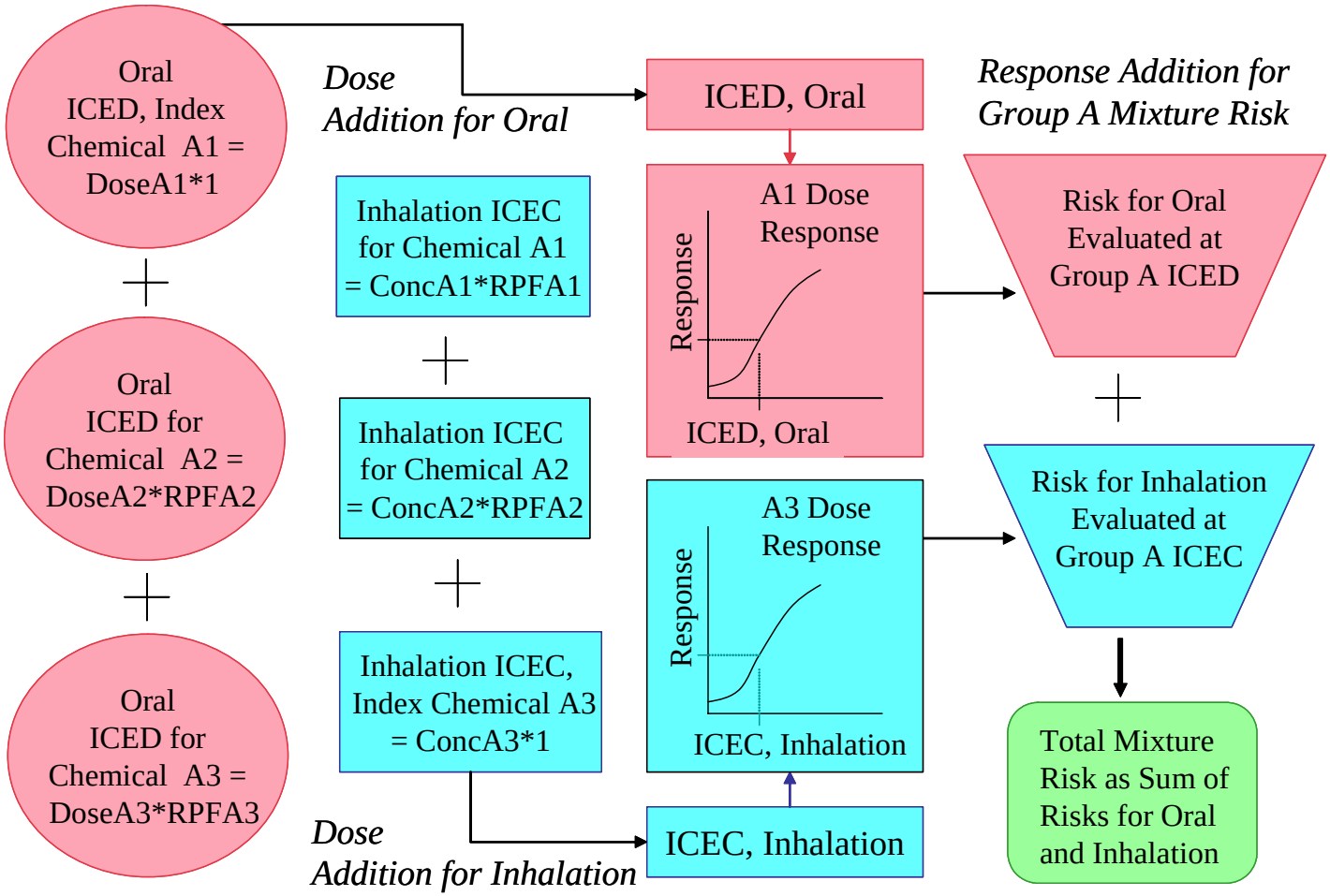


FIGURE 4-12

Combining Grouped RPF Estimates Across Exposure Routes
(Source: U.S. EPA, 2000e)

(1) Component ICED - refers to the ICED for an individual chemical

(2) Group ICED - refers to the ICED for all chemicals within the group and route, formed by summing the component ICEDs.

The RPF approach has been proposed for characterizing health risks associated with mixtures of chemicals that are toxicologically similar (U.S. EPA, 2000a). To develop an RPF-based risk estimate for a class of chemicals, good toxicologic data are needed for at least one component of the mixture (referred to as the index chemical). Scientific judgment and analysis of available data are used to assess the relative toxicityof the other individual components in the mixture. The component ICEDs are then summed within the group to generate a route-specific ICED. The risk posed by the group and route of interest can be estimated using the route-specific dose- response information for the index chemical. For each exposure route, the RPF approach uses dose-addition to estimate risk for the toxicologic outcome common across the group. An assumption is made that the route-specific risks are independent of each other (i.e., the toxicity caused by one route does not influence the toxicity caused by the other route). This condition meets the criteria required to apply response addition; the route-specific risk estimates are added to yield a risk estimate for the mixture group. Quantitative uncertainty analyses of this approach are complicated by the general lack of multi-route toxicity studies. It is then important during the toxicity assessment to identify any studies or dose-response data on the multi-route mixture exposure that can support this RPF approach.

4.7.2. Internal Dose Estimates. A third quantitative approach to handling mixtures assessments for multi-route exposures is to estimate a total internal dose for use in risk estimation. In 2003, U.S. EPA completed a report showing that a multi-route mixtures

risk assessment can be conducted based on internal dose estimates developed in both test animals and humans for toxicants that do not cause portal of entry effects (Teuschler et al., 2004; U.S. EPA, 2003b). This approach is mentioned here for completeness but is resource intensive.

U.S. EPA (2003b) combines exposure modeling results, PBPK modeling results, and the RPF mixtures risk assessment approach. Human internal doses (e.g., blood, tissue, and organ concentrations) were estimated using PBPK models, accounting for external exposures from multiple routes (as dictated by the exposure scenario) and human PK processes. Hypothetical RPFs were developed for a subset of chemicals based on test animal data. Although the application of a full PBPK model was recognized as the preferred approach to estimating rodent internal doses (i.e., blood concentrations), for the example data used in the report, administered doses were assumed to be 100% bioavailable to the rat. The rodent toxic effects were assumed to be constant between internal and external exposures and were used to evaluate the human dose-response relationship. The use of internal dose measures (i.e., blood concentrations in both humans and rodents), both for developing the RPFs based on rodent data and for indicating human multi-route exposure, provides a consistent basis for extrapolating across species. However, it should be noted that these approaches are inappropriate for use with toxicants that elicit responses at points of contact with the body (e.g., skin, intestinal tract, and nasopharyngeal, bronchial and lung epithelia).

4.8. SUMMARY RECOMMENDATIONS

The toxicity assessment step includes the evaluation of all available and relevant toxicity data, with the goal of simplifying the multiple chemicals, exposures, and effects.

The approach presented here focuses on the identification of common characteristics so that these multiples can be consolidated into a manageable number of groups. Because the primary risk methods invoke dose addition or response addition, the grouping processes focus on assumptions of toxic similarity or toxic independence, respectively. As the chemicals, pathways, and effects are grouped, it is critical to include a discussion of the evidence supporting those key assumptions. Any decisions to exclude chemicals or exposure pathways from the cumulative risk assessment must be supported by toxicity arguments that are highly relevant to the estimated exposures. When such information is weak, the chemicals and pathways should be retained in the assessment.

5. CUMULATIVE RISK CHARACTERIZATION

The last phase of cumulative risk assessment, risk characterization, assembles all the information from the analysis phase and interprets the results in the context of the problem(s) formulated in the planning and scoping phase. As described in Agency guidance (U.S. EPA, 2000f), risk characterization should include two products, an *integrative analysis*, which can be fairly technical, and a *risk characterization summary* that emphasizes recommendations and uncertainties. Text Box 5-1 describes some important elements of a risk characterization that are useful to consider in a cumulative risk assessment. As presented in Chapter 1, cumulative risk assessment includes all aspects of the traditional risk assessment paradigm (i.e., hazard identification, dose-response, exposure assessment, risk characterization). However, these concepts must be integrated and expanded beyond the elements included for both single chemical and mixture risk assessments to account for the complexity of cumulative risk (U.S. EPA, 2000a, 2003a). In this document, cumulative risk assessments potentially include multiple chemicals, multiple exposure routes and pathways, multiple toxic effects over various time frames, joint exposure response relationships, and population based risk estimates. Figure 5-1 illustrates these

Elements of Risk Characterization *(Text Box 5-1)*

* Quality of and confidence in the available data;
* Uncertainty analysis;
* Justification of defaults or assumptions;
* Related research recommendations;
* Contentious issues and extent of scientific consensus
* Effect of reasonable alternative assumptions on conclusions and estimates;
* Highlights of reasonable plausible ranges;
* Reasonable alternative models; and
* Perspectives through analogy.

(U.S. EPA, 2000f)

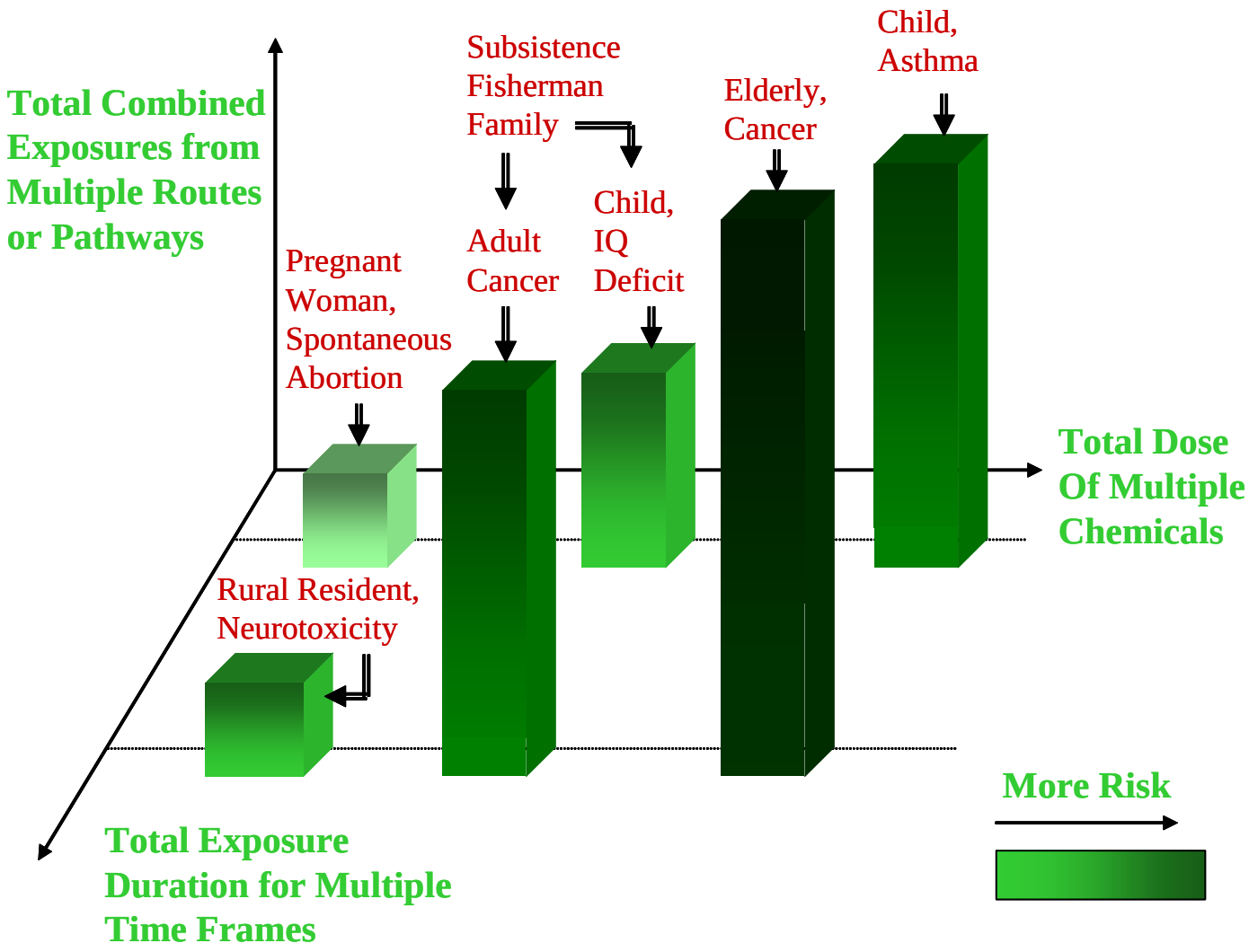


FIGURE 5-1

Consideration of Multiples in Cumulative Risk Analysis

concepts using a three-dimensional diagram in which the darker shaded bars represent higher risk. The vertical axis represents increasing exposures from multiple pathways and routes. The axis coming forward on the page represents increasing exposure duration for multiple time frames. The horizontal axis represents increases in total dose from multiple chemical exposures. The shaded bars show the potential for multiple effects of combined exposures, multiple chemicals and exposure duration for the following vulnerable subpopulations:

- Pregnant woman – Spontaneous abortions from short-term, multiple route exposures to low doses of multiple drinking water disinfection by-products (Waller et al., 1998)
- Rural resident – Neurological effects from chronic multiple route exposures to organophosphorous pesticides used in agriculture (U.S. EPA, 2002a)
- Subsistence fisherman family – Cancer in adults exposed chronically via ingestion of fish containing PCBs (U.S. EPA, 1996b); IQ deficits in children exposure *in utero* to methyl mercury via fish consumption (U.S. EPA, 1997e)
- Elderly – a potential combination of high exposure and high vulnerability is shown by a susceptible population (e.g., the elderly) that may be more vulnerable to a health effect (e.g., cancer) from chronic, multiple route exposures to high doses of multiple chemicals (U.S. EPA, 2003a)
- Child – asthma from short term inhalation exposures to high levels of particulate matter in the air (U.S. EPA, 2004e)

Thus, the cumulative risk characterization must consider multiple risk factors as identified in the initial planning and scoping phase.

The risk characterization phase is critical to the interpretation and communication of the cumulative risk assessment process and results. In the usual risk characterization, the major scientific evidence and "bottom-line" results from hazard identification, dose-response assessment, and exposure assessment are evaluated and integrated into an overall conclusion about risk,

along with clear descriptions of the limitations and uncertainties (NRC, 1983, 1994). In cumulative risk assessments, these same steps are included but, because of the multiples described above, the evaluations are more complicated, making it more difficult to identify and understand the implications of the assessment results. Text Box 5-2 shows an example of this complexity. Successfully communicating the uncertainties can then be a major challenge.

The development of the risk assessment is typically an iterative process, where information from each process step is reconsidered from the perspective of the information generated during the other steps. The analyst evaluates the collective information, identifying information gaps, uncertainties at the interfaces between different process steps, and the appropriateness

Example: Site Closure vs. Public Access *(Text Box 5-2)*

Consider a site with soil contamination where the decision alternatives are open public access and full closure (clay cap and fence). The risk assessment is then to address the public access scenario, where unacceptable risk would suggest the need for site closure. The complications discussed here include population-dependent exposure characteristics, for example the population near the site may include adults and children with quite different exposures. For this case, children are assumed to be exposed predominantly by direct contact with soil (dermal and ingestion) ar adults primarily by inhalation of dust. Both subgroups might also b exposed by ingestion at lower concentration levels, mainly of groundwater that is contaminated from gradual migration through the soil.

Complexities to Consider when Determining Risk:

- Different proportions of chemicals in inhaled dust compared with ingested groundwater, leading to different critical effects and different toxicologic interactions
- Different toxic sensitivities of adults versus children
- Time-varying combined exposure from soil and groundwater that reflects multiple routes as well as timeframes

The integrative analysis should evaluate the relative impact of eac of these complexities on the cumulative risk estimates. Any joint contributions to risk should be quantified to the extent possible based on available information.

Risk Characterization Summary:

- Usual elements of the risk characterization (summary of likely health endpoints, identification of key chemicals)
- Comparison of adult risk with child risk for all routes combined and over different exposure routes and timeframes
- Quality of the exposure estimate from combining across route
- Quality of the toxicity information for children and adults
- Confidence in summary estimate of cumulative risks.

Other descriptions that might be required for this example site include a comparison of the risk for average exposure vs. high-en exposure (for adult and for child) and the ranking of the most influential factors driving the risk estimates (a quantitative sensitivi analysis if possible).

of the different levels of analysis across the steps of the risk assessment. For example, combining dose-response and exposure data that are in different units forces the use of assumptions or new data gathering.

An important iteration is the comparison of the analysis results with the goals set out in the problem formulation stage. Once again, the description of uncertainties plays a pivotal role, in this case to help determine whether these goals have been met. If the results do not sufficiently address the goals, an iteration through one or more of the previous steps might be indicated, including the initial scoping and problem formulation.

An important aspect of cumulative risk assessment is the process of identifying and defining geographic areas, groups of chemical, biological and physical agents, and exposure scenarios that are judged to either require or not require further analysis. These decisions about the conduct of the assessment expand further to take into account appropriate groupings of chemical agents using exposure information (Chapter 3) and judgments regarding similarity of toxic effects and the potential for interactions (Chapter 4). Broader elements should also be addressed in the risk characterization: appropriateness of the analytic selected scope, choice of agents for analysis, choice of exposure scenarios, criteria for grouping chemicals, and identification of appropriate populations for analysis. At the end of this process, the analyst identifies the types of effects that might occur, quantifies their likelihood in different populations, and quantifies the uncertainties in these estimates. Any effects or risks that cannot be quantified are to be described qualitatively, along with suggestions for the kind of information required for quantitative characterization. The principles and guidance offered in the *Policy for*

Risk Characterization (U.S. EPA, 1995b) and *Science and Judgment in Risk Assessment* (NRC, 1994) are applicable to characterizing cumulative risks.

Various individuals and groups may be significantly impacted by the results of the risk characterization. As discussed earlier, potential stakeholders might be represented by industry scientists and decision-makers, local government representatives, local residents, citizen action groups, national environmental advocacy groups, and national industry advocacy groups. Some issues with which they may be concerned include the number of people exposed, the range of uncertainty around the exposure and health risk estimates, the critical variables driving the assessment, the existence of data gaps, the bottom-line conclusion, and whether the risk characterization supports a regulatory decision. The economic and social ramifications of cumulative risk assessments require that the risk characterization communicate the results clearly, highlighting the important issues and uncertainties and exploring their implications for different audiences. The risk characterization should focus on transparency in the logic that leads to decisions regarding the inclusion or exclusion of specific exposure pathways, specific chemical classes or groups of agents, and specific risk characterization approaches. The consistency and reasonableness of the assumptions used to group chemicals for use in risk assessment procedures also need to be evaluated. As discussed in the mixtures risk guidance (U.S. EPA, 2000a), any quantitative or qualitative risk estimates must be accompanied by the discussion of uncertainties and assumptions.

These obligations of risk characterization apply to all risk assessments conducted by U.S. EPA. Issues unique to, or more complex in, cumulative risk characterization are discussed in the following sections.

5.1. SPECIAL CONCERNS WITH CUMULATIVE RISK CHARACTERIZATION

The EPA guidance documents on risk characterization all present lists of issues or questions that should be addressed in the risk characterization step. As mentioned above, the expansion to cumulative risk adds certain complexities, which change the questions to be addressed. These lists usually include three major areas:

- What is the simplest description that captures all the critical information?
- How are the specific technical aspects addressed? and
- What are the policy and technical choices or alternatives for the cumulative assessment?

There are issues that are usually inappropriate for a cumulative risk characterization: identifying a single key, supporting toxicity study; addressing only one critical effect; and deriving a single benchmark risk value with which to judge safety of exposures. The following list of questions may be used to guide the analyst in developing a cumulative risk characterization. It covers most of the issues in the risk characterization handbook (U.S. EPA, 2000f, Chapter 3) and is grouped according to the characteristics that differ most with cumulative risk. (Several of the methods discussed are in Chapters 3 and 4.)

To Address Multiples:

Is there a focus, e.g., an effect caused by a single chemical by one pathway, that dominates the risk? If no single key factor dominates, then what is the best presentation of the array of possible combinations of factors?

How do composite evaluations compare with multivariate measures? How much detail and accuracy is lost when combining across effects, such as with ordinal regression? How well supported are the number of assumptions and default

parameters that are used, and how can that strength of support be reflected in the quantitative risk characterization?

How does the use of surrogates affect the overall uncertainties? How does relying on an index chemical to represent the group increase the uncertainties surrounding the contributions of the other chemicals?

Grouping chemicals, pathways, and effects structures and simplifies the assessment. Are there alternative ways of grouping these factors? Are any factors double-counted by the grouping process?

To Address Interactions:

Can the interaction magnitude be estimated for those chemical-pathway combinations of most importance? How many interactions cannot be quantified? Can all identified interactions at least be described for the direction of the interaction, i.e., do they increase or decrease the risk?

To Address Populations of Concern:

How consistent are the risk estimates with those health effects of most concern to the stakeholders as determined in the planning and scoping step? If a health effect was the trigger or impetus for the cumulative risk assessment, is that effect adequately addressed in the risk characterization?

To Address Time Dependencies:

What is the likelihood that the mixture composition or exposure pathways will change over the timeframe being addressed? Can the impact of that change be quantified in terms of a change in risk?

How likely is it that the subpopulations of most concern will change location and thus, change their risks over the timeframe being addressed?

Will any of the alternative remediation options change the mixture composition (not just the total dose)? Is that change reflected in the way the expected reduction in risk is calculated?

To Address Consistency of Information:

How well do the exposure levels in the dose-response data match the estimated exposure ranges?

How much extrapolation is required for the risk estimates? How dependent is the extrapolation on default values?

Are there inconsistencies among the data? Do some exposure or toxicity units need conversion in order to allow combined exposure or joint toxicity to be estimated? How different are the exposure and toxicity measures in terms of level of understanding, level of accuracy, and detail? How much information is lost when reducing all the measures to the lowest common level so that grouping and composite analysis can be performed?

To Address Context:

How can the risk characterization for this site or situation be compared with risk characterizations for other similar sites or situations? How can multivariate site descriptions and risk evaluations be compared to determine whether sites are similar to each other?

5.2. EXAMPLE EVALUATIONS OF QUANTITATIVE APPROACHES TO CUMULATIVE RISK CHARACTERIZATION

Much of the process of cumulative risk assessment involves information sharing, planning discussions, and qualitative or judgment based decisions. As with all U.S. EPA risk assessments, there is also the potential for quantification of exposure and risk. Because cumulative risk assessment includes many factors, some of which vary over time, the ideal risk calculations would utilize supporting measurements and studies that usually do not exist. For example, Section 4.7.1 presents a modified relative potency factor (RPF) approach for exposure to mixtures by multiple pathways. The RPF approach requires information demonstrating that the chemicals included in the calculation have similar toxicologic modes of action. Such information is not always available on all chemicals of concern. Some of the quantitative approaches presented in Chapter 4 are examined here in terms of feasibility and impact on the risk assessment.

5.2.1. Example Cumulative Risk Characterization: Cumulative Hazard Index. As an alternative to the RPF approach of Chapter 4, the integration of multiple chemical exposures along multiple pathways can be quantitatively represented in a simple fashion by the cumulative hazard index (CHI). The common dose-additive hazard index (HI) combines multichemical exposures by summing the component exposure levels after each has been scaled by division by that chemical's reference dose (RfD, for ingestion) or reference concentration (RfC, for inhalation). (See Section 4.2.1 for a complete description of the dose-additive HI.) The CHI is defined here to be similar to the basic Superfund cumulative HI. The Superfund guidance first recommends calculating each chemical's exposure for each completed pathway and then converting

each into a pathway-specific, or more properly, a route-specific hazard quotient (HQ) in the usual way. EPA's Risk Assessment Guidance for Superfund (1989a) instructs risk assessors to sum HQs (Equation 5-1) across exposure routes and exposure pathways, providing there is evidence of combined exposure pathways to identifiable individuals or groups of individuals who would consistently face a reasonable maximal exposure. For each chemical, the pathway HQs are summed to give the risk characterization reflecting that chemical's total exposure to the individual or population, and expressed as a total HQ across exposure routes with those routes explicitly stated. The CHI is then the sum of these totals across chemicals.

5.2.1.1. Calculation Steps — The CHI calculation that follows is based on the Superfund guidance (U.S. EPA, 1999b).

This equation solves for pathway-specific HQ for chemical j:

$$HQ_{jk} = E_{jk} \Big/ RV_{jk} \qquad (5\text{-}1)$$

where:

k = one of the pathways

E_{jk} = exposure for that pathway and

RV_{jk} = the risk-based toxicity value for pathway k, such as the RfD for the water pathway or the RfC for the air pathway.

This equation solves for total HQ for chemical j across m pathways:

$$HQ_j = \sum_{k=1}^{m} HQ_{jk} \qquad (5\text{-}2)$$

The CHI across pathways and chemicals is then the sum across chemicals of the total HQs:

$$CHI = \sum_{j=1}^{n} HQ_j \qquad (5\text{-}3)$$

where n is the number of chemicals in the assessment. Not all chemicals need to be present in a given pathway, and a given chemical need not be present in all pathways. This latter condition means that in Equation 5-2, some terms might be zero.

5.2.1.2. Interpretation — The numerical value of CHI is an index of concern in the same vein as the common dose-additive HI used for mixture risk characterization. The numerical value should not be interpreted as a risk number. For example, although a higher CHI value indicates more concern for possible health effects, CHI=8 does not necessarily indicate a site hazard that is 4 times worse than if CHI=2. The purpose of the CHI is to express the degree of concern over possible toxic effects from onsite exposure.

As with the mixture HI, the value of 1 could be used as the decision point for determining whether further assessment or remedial action is warranted. When CHI>1, the quality of the CHI should be examined. (Issues with CHI<1 are discussed below.) The exposure assessment should be evaluated to determine any changes if more details are available, such as information suggesting co-exposure by multiple pathways. The dose-response assessment should be reviewed, particularly the assumptions of similarity and no interaction (see Section 5.2.1.3), along with the other assumptions described in the U.S. EPA mixture guidance (U.S. EPA, 2000a). As with the mixture HI, if CHI is only slightly greater than 1 (say, CHI=3) then the uncertainties in the methodology might exceed the numerical precision of the index. If CHI greatly exceeds 1, then there might be significant concern for health effects and the exposures should be further evaluated for possible remedial action.

When CHI<1, the indication is that no significant hazard exists by the chemicals and pathways addressed. The key assumption to be checked is "no interaction." If any indication of synergy exists from the supporting toxicity studies, then the pathways involving those interacting chemicals should be evaluated in more detail. The second check to be made is of the uncertainties, in particular the missing information (see Section 5.3 for more details and suggestions).

Note that because the CHI involves simple sums, the summation can proceed in either order:

- either first sum across pathways for each chemical and then across chemicals (Superfund's approach, given above in Equations 5-2 and 5-3) or
- first sum across chemicals to get a pathway specific HI and then sum HIs across pathways.

The first sequence of summing gives an index of total risk per chemical and thus identifies which chemicals are posing the highest hazard or risk. That approach might be useful in predicting the toxic effects that are most likely or of highest severity, keying on the critical effects of those chemicals.

The second sequence gives an index of total risk per pathway, which might assist in determining the preferred remediation approach. That approach might suggest focusing on treating or mitigating the high risk pathway, without paying much attention to the specific contaminants in that pathway. The best approach might be to perform both intermediate calculations and present both the highest risk chemicals and highest risk pathways to the decision makers. Previous experience by U.S. EPA in risk assessments of Superfund waste sites indicates that in many cases risks will be dominated by one or two chemicals and by one or two exposure pathways. These two intermediate calculations will then help explain the extent of that dominance and provide

support for further simplification or reduction in the scope of the cumulative risk assessment.

This calculation is analogous to the cumulative risk approach used by the U.S. EPA Office of Pesticide Programs (OPP). Although OPP uses margins of exposure (MOEs) instead of HQs, once they are scaled by an uncertainty factor for species differences, the total MOEs become nearly identical to the inverse of the total HQ. The primary difference is in use of uncertainty factors. OPP considers whether there are deficiencies in the database that apply to the chemicals as a group. The concern is tied to the FQPA legislation that requires an additional safety factor when children's health is an issue. If evidence indicates that another critical effect is produced by the identified mechanism of toxicity at a dose significantly lower than those used in the risk approach, then an additional database uncertainty factor is applied to the mixture assessment to be protective for the young. OPP notes the importance of only applying an uncertainty factor for database uncertainties once, i.e., either to a specific individual chemical or as a group factor (U.S. EPA, 2002d).

5.2.1.3. Assumptions with CHI — The risk characterization step should address the assumptions in the CHI determination and the likely conditions under which the approach would be reasonable and those under which it would be inappropriate. Similar to the use of the mixture HI (U.S. EPA, 2000a), the CHI is useful for a screening level risk assessment because it is fairly simple to determine once the exposures have been estimated. The simple summation carries with it two assumptions:

- There are no interactions across exposure pathways or chemicals in terms of toxicity and

- There are no interactions across chemicals in terms of fate and transport or in terms of single or multiroute uptake by the exposed individual.

The main weakness then seems to be this assumption of no interactions. By drawing analogies to mixture risk procedures, one can define conditions under which this exposure additivity, i.e., the lack of interaction, is plausible. The chemical properties under which the HI for mixtures risk is plausible all relate to concepts of functional or structural similarity. The counterparts for the CHI are:

- Each of the chemicals incorporated into the CHI should be toxicologically similar for all of the pathways included in its pathway HQ calculation and should have no significant portal of entry effects (route-specific primary toxicity). Similarity here can be indicated by the same toxic mode of action, same primary target organs, or similar general type of toxic effect (e.g., cancer, reproductive toxicity). (For further discussion of toxic similarity, see Section 4.5). This property supports the combining of exposures across pathways because for a given chemical, the same main toxic effects occur for all pathways.

- The chemicals grouped for a given pathway should be toxicologically similar for that pathway according to the requirements for dose addition. This property supports the combining of chemicals for a given pathway, i.e., the pathway HI.

- Perhaps most unique to cumulative risk assessment, the chemicals should not affect each other's fate and transport, regardless of pathway.

Text Box 5-3 shows an example illustration.

5.2.2. Ordinal Regression Calculations for Multiple Effects and Pathways. One complication of cumulative risk recognized in the Agency's *Framework* (U.S. EPA, 2003a) concerns the risk estimation and communication of multiple toxic effects. The inclusion in the risk assessment of multiple stressors, pathways, exposure timeframes, and subpopulations increases the likelihood of multiple effects of concern. One approach is to separate the risk characterization into parts so that each part addresses only one of the likely toxic effects. This approach would provide a fair amount of detail

that may be more difficult to incorporate into a risk management evaluation, partly because the differing effects would need to be ranked in order of public health concern. An alternative is to address the multiple effects directly in a single composite measure as described in Chapter 4.

Example: Site Safety *(Text Box 5-3)*

Consider the case where a goal is to be able to decide with high confidence whether the site is safe as is. Then one risk description could include an overly conservative (health protective) estimate, perhaps one based on the high end exposure estimates for each of the possible routes. If this conservative risk estimate is considered to be within acceptable levels, then any improved risk estimate is likely to be lower, indicating high confidence of no health concern. For risk characterization described by the CHI, then if CHI<1, this screening level conclusion is there is no health concern.

This approach is similar to the screening calculation of a Hazard Index that includes all chemicals, temporarily ignoring the requirement of same target organ: if the mixture's screening assessment gives HI<1, even when including all target organs, then there is a conclusion of no health concern because an improved and more appropriate HI restricted to a specific target organ would be even lower (U.S. EPA, 2001d). If CHI>1, then additional evaluation is recommended. Because the CHI is a conservative overestimate of the hazard index, a value exceeding the criterion does not imply the expectation of toxic effects but only that a more detailed risk assessment is needed.

Note that for decisions on safety, the screening criterion might be smaller, say CHI=0.5. Using a smaller index criterion would assure more confidence that there is no significant health concern. On the other hand, a smaller criterion also increases the number of times the decision will be to gather more information and perform a more detailed risk assessment.

5.2.2.1. Calculations —

Two formulas are given in Chapter 4 (see Section 4.5.1) for describing multiple effects and are restated here, one based on the HI (Equation 5-4) and one based on response addition (Equation 5-5):

$$HI(effects) = \sum_{i=1}^{n} \left(\frac{E_i}{BMDL_i / UF_i} \right) \qquad (5\text{-}4)$$

and

$$R_m(effects) = \sum_{i=1}^{n} P_i(severity > 2) \qquad (5\text{-}5)$$

or more accurately as

$$R_m(effects) = 1 - \prod_{i=1}^{n} P_i(severity \leq 2) \quad (5\text{-}6)$$

where:

BMDL = Benchmark dose lower bound

UF = Uncertainty factor.

Equation 5-6 is the general form of Equation 4-2, response addition for only two chemicals. As with the common response addition for mixtures, Equations 5-5 and 5-6 become essentially identical for low risks, say P_i <0.01. The representation in Equation 5-6 might be easier to follow because its factors are the results of categorical regression as given in Equation 4-3.

Details are provided in Chapter 4, but the basic concepts are fairly simple. In both formulas, the underlying dose-response data, which include all effects of concern, are first converted into dose-severity data by assigning each effect to a severity category, where categories 3 and 4 represent toxic or lethal effects. In Equation 5-4, the benchmark dose lower bound (BMDL) is derived from categorical regression on the dose-severity data, and represents the dose associated with a fixed low probability of toxicity, e.g., P(severity>2)=0.10. The BMDL is scaled to human terms by the uncertainty factor so that the denominator is similar to the RfD and the formula corresponds to the standard mixture HI formula.

The HI(effects) calculated in Equation 5-4 could be used in the CHI calculation of the pathway HI, and would then avoid the need to assume toxic similarity of the chemicals in that pathway. Because all effects are included, the pathway HI and the resulting CHI would also reflect all effects in the underlying dose-response data.

In Equation 5-5, the first step is to convert the doses in the supporting toxicity data into human equivalent doses. That converted set of dose-response data is then modeled using categorical regression, as described above (and in Section 4.5.1). The resulting regression formula is then used with the actual exposure estimates to generate probabilities or risks of toxic effects (i.e., severity>2). The risk for the mixture is then given by the sum of these chemical-specific risks. The mixture risk is not attached to any particular toxic effect, as is the common single chemical benchmark risk, but instead reflects all toxic effects in the underlying dose-response data and is then the risk or probability of any toxicity. This risk addition approach is fairly easy to interpret for a mixture of chemicals in one pathway or environmental medium, i.e., examining the assumption of independent toxic action among the chemicals. For this regression on overall severity, this assumption might be described as the toxicity of one chemical having no effect on the toxicity of another chemical in the mixture, which is more plausible if the component doses are all low. The combined mixture risk is then an estimate of the probability of toxicity (any effect) from one or more of the chemicals. The extension to cumulative risk in terms of a combination across pathways is not as clear.

5.2.2.2. Assumptions with Multiroute Formulas for Multiple Effects — The calculation formulas for hazard or risk for multiple effects by multiple routes are similar to their counterparts for simple mixtures, but the assumptions are less clear and more difficult to evaluate. For Equation 5-4, the use of an HI implies the assumption of similar toxicity across the chemicals. The regression on all effects makes the interpretation more complex. Because the BMDL indicates a specific risk of toxicity, the HI represents

an increasing concern as more chemicals approach or exceed their benchmark risk level. The combining of multiple lower confidence bounds on the benchmark dose has not been sufficiently investigated to allow a probabilistic interpretation in terms of a confidence bound on the HI calculated in Equation 5-4.

Both of these approaches for addressing mixture risk for multiple effects are new and have not been implemented in actual site assessments. One aspect related to screening level assessments is the decision to base probabilistic risks on severity>2, which means overt toxic effects. If a more conservative approach to the screening assessment is indicated, then the calculations could be based instead on severity>1, which would include definite effects that are not necessarily adverse. Further exploration of the numerical properties of these approaches and scientific assumptions with respect to transport and toxicity are encouraged.

5.2.3. Combination of Exposures of Different Time Frames. Risk estimates for different time frames must consider the combined dose-duration influence on toxicity. With complex aggregate exposures, the overlapping of exposures that have quite different time courses is possible. An example is a low continuous exposure (say, ambient air and drinking water) combined with intermittent exposure to industrial pulse emissions, perhaps once a week at moderate to high levels. For acute exposure to many chemicals, peak tissue concentration seems most appropriate as a predictor of toxicity, i.e., accumulated dose or simple time-weighted averaging does not work (Boyes et al., 2000). For longer exposure periods, simple cumulative dose (Haber's rule) often does not work although a modified form does seem acceptable as a dose-

duration metric. The combining of joint exposures over differing time frames then must use the exposure metric appropriate to each exposure period.

The Agency and various scientists have published guidance, issue reports, and research results on the impact of exposure duration on toxicity but so far only with respect to single exposures for a fixed duration (Miller et al., 2000; Strickland and Guth, 2002; U.S. EPA, 1998d, 1999d, 2000c, 2004f; Zwart and Woutersen, 1988). The complication with cumulative risk assessment is the potential overlap of exposures, the durations of which differ. The combination exposures should be evaluated jointly, as described in Chapters 3 and 4. When an exposure is short, less than a few days, then the following steps are recommended:

- Estimate the combined exposure during the short exposure period, based on the combination of the short and longer exposures. For example, a brief exposure to a hepatic toxicant might be combined with a longer term exposure to another hepatic toxicant by summing their exposure levels, to give a higher exposure level for the short duration.

- Develop a risk characterization specific to this short exposure period, focusing on those significant effects that do not persist beyond the short exposure period.

- Determine whether any effects from the short exposure are likely to persist well into the longer exposure period. Those effects should be incorporated into the description of likely toxicity for the longer period. The persistent effects might be increased by the longer exposure and might influence other effects caused by the longer exposure.

5.3. DESCRIPTION OF RESULTS

The risk characterization should include a summary or overview description of health risk to the population of concern along with a second description that provides more details. The goals defined in the problem formulation stage might dictate additional descriptions or options.

5.3.1. Risks for Population of Concern. The population of concern is one of the items defined in the planning and scoping phase. The risk characterization for that population is then a key result of the risk assessment and should at least include the description of risk or expected toxicity for the average population exposure, along with the size of the population. Because the assessment applies to the population as a whole, this result can serve as a clear summary of the risk assessment. There is a tendency, however, to describe such risks in simple, often one-dimensional terms. In a cumulative risk assessment, however, complexity is expected. Because the setting includes multiple chemicals with exposure potentially by multiple routes and time frames, the number of health effects to be addressed can be quite high. For example, even if one only described risks for the critical toxic effects, ignoring secondary effects and joint toxicity, there can be different effects for each chemical, by each route, and for each time frame of exposure. Moreover, the potential for several sensitive subgroups means that the distribution of effects and severities to consider can be quite broad.

The cautionary advice most often given for cumulative risk characterizations is to be clear and avoid oversimplification. With sufficient information, each of the parameter combinations could be assessed separately, resulting in a distribution of risks that covers the range of combinations of exposure and population subgroup. In many cases, however, the information required for a complete quantitative risk characterization of these combinations will be unavailable. At the least, the assessor should provide a recommended risk estimate for the population, such as a central or median risk estimate for the average individual, along with a risk estimate for the high end of the population risk distribution. The high end risk characterization must clearly

describe the assumed conditions leading to that high risk. Of particular importance is the plausibility of the co-occurrence of the many factors related to the high-end risk. For example, the risk of a given daily oral exposure might be highest for a child because of the low body weight. The risk for an exercising adult (all else being equal) might be highest because of the high daily drinking water intake. For a plausible high-end risk estimate, the child body weight should be combined with the child daily intake and similarly for the adult; it would be unrealistic to combine the two extremes: a low body weight (e.g., the 10-kg child) with a high daily oral intake rate (e.g., the exercising adult).

The multiplicity of potential health effects in a diverse population raises another complexity issue: the presentation or evaluation of the combination of different effects. The traditional approach using a single critical effect avoids this issue so that the population risk can be attached to one type of toxic endpoint, e.g., reproductive effects. With cumulative risks, there may be several toxic effects of differing severity and with different ways to measure or describe them, including some quantitative and some judgmental. One approach described earlier (Chapter 4 and Section 5.1) relies on converting the observed effects into a small set of severity categories, so that different effects can be compared based on their toxic severity. Another approach is to simplify the effects description by tying the risks to toxicity groups (see Chapter 4 and Appendix B). In either case, the presentation of results must include a list of all effects addressed by each risk measure, along with a discussion of the more likely effects. Because of possible differences in exposure durations and treatability of the effects, the discussion should also include any information on the persistence or reversibility of the most likely effects.

5.3.2. Risks for Population Subgroups. Specific population subgroups of main concern might be identified in the planning and scoping stage. Some subgroups might be linked to the trigger that led to the cumulative risk assessment although other subgroups might also be of concern. For example, proposed siting of a chemical manufacturing plant might be nearest to the population subgroup that initially raised the issue, while emissions could disperse to cause wider-spread exposure. Those subgroups identified in the scoping phase must be included in the risk characterization. Results should be described in terms of the factors decided in the problem formulation phase to ensure that the questions of central concern to the stakeholders have been answered.

Several sensitive population subgroups might be identified during the exposure and toxicity assessment steps. The risks to these subgroups should be described along with estimates of the size of each subgroup, for completeness as well as improved information for the risk managers. For example, remediation of organics in groundwater by air stripping should be designed to avoid increasing risk to other sensitive subgroups, such as nearby children living downwind.

5.3.3. Important Interaction Factors. The risk characterization will be used to decide from among several risk management response alternatives, from recommended changes in individual lifestyles of the affected population to official governmental action. These responses often will involve changing one or more factors in the scenario. For example, a remedial action could include moderate reduction of all exposures or substantial reduction of some key exposures. Because the cumulative risk assessment considers interactions (e.g., in transport and toxicity), those same interactions will affect

the post-remediation risk assessment. Any remedial decisions will be enhanced if the key interactions are identified and discussed in the risk characterization. Summaries that only indicate the direction of potential interactions, i.e., greater or less than dose addition (see Table 5-1), might still be useful for setting priorities or changing the degree of conservatism used in the assessment.

One issue related to interactions, or at least to multiple sources contributing to joint toxicity, is site-related (or source-related) exposure levels compared with background exposure levels. Site contamination is often translated into the incremental exposure, and thus incremental risk, i.e., the risk from the site exposure that exceeds background. If background levels are comparable, and slightly toxic (e.g., above the RfD for oral exposures), then the inclusion of background exposure into the cumulative exposure estimate is appropriate as another source. When background exposure contributes little to the cumulative risk, then separating the risks by background vs. the site can add to the information needed for remedial action decisions.

5.4. DISCUSSION OF UNCERTAINTY

Clarity and transparency are requirements of cumulative risk assessments. For risk descriptions, this relates to uncertainties and variabilities in the process and calculations used to estimate the risks. Uncertainty refers to lack of knowledge, such as unidentified chemicals in a groundwater sample or lack of data for modeling the differences in toxicity between test animals and humans. Variability is used here to denote known changes in certain important factors, changes that may or may not be measured, and the impact of these changes on risk may not be quantified. Both uncertainty and variability should be addressed quantitatively to the extent possible.

TABLE 5-1

Joint Toxicity: Summary of Pairwise Toxic Interactions by Organ/System*

Metal Interactions	Blood	Kidney	Neurologic	Male Reproductive	Skin	Cardio-vascular
Higher than additive			As+Pb Cd+Pb	Cd+Pb	Cr+As	As+Cr
Additive		As+Cd				Cd+Pb
Lower than additive	As+Cd As+Pb Cd+Pb	As+Cd As+Cr As+Pb Cd+Pb		As+Cd		

* As=arsenic, Cd=cadmium, Cr=chromium, Pb=lead. All exposures are oral. This table summarizes information in Table 4-2. (Data from ATSDR, 2004)

When only qualitative characterizations are provided, their bases should be described along with suggestions for ways to improve and quantify those characterizations.

As has been discussed in several previous U.S. EPA risk assessment guidance reports, a critical part of the uncertainty analysis concerns the possible impact of missing information. For example, if the risk assessment produces CHI<1, that might not indicate safety if important information is not included. Instead, the CHI calculation should be evaluated and quantified where possible for the likely change if the missing, critical information were obtained. One example approach treats the possible impact on a mixture risk estimate from unidentified chemicals in drinking water (U.S. EPA, 2003b). Chemicals and exposure pathways that are not quantitatively included in the risk assessment should be placed in a watch list, so that when sufficient information becomes available, their contribution to the cumulative risk can be assessed.

5.4.1. Environmental Media Concentrations and Population Contact. The exposure scenarios developed for a cumulative risk assessment involve multiple chemicals and multiple environmental media. The concentrations of these chemicals in various environmental media may be estimated through direct analytical measurement, predictive modeling, or some combination of the two. The sensitivity and specificity of different analyses used to measure the concentration of different chemicals or the same chemicals in different media should be carefully evaluated. The quantitative uncertainty of model predictions for concentrations of chemicals in different media may also vary. When combining information on chemical concentrations in the characterization, clear identification of the limits of the techniques used to estimate these concentrations is necessary.

Ingestion, inhalation, and dermal contact rate information may be developed from several different sources. The U.S. EPA *Exposure Factors Handbook* (U.S. EPA, 1997c) recommends specific ingestion rates for foods such as vegetables and freshwater fish, and drinking water. The relevance of the rates from these recommended studies to the populations being evaluated should be examined. For example, freshwater fish consumption rates among individuals in certain Native American tribal groups may be greater than those in the general U.S. population (e.g., Peterson et al., 1995; Toy et al., 1995).

Finally, an exposure in a traditional risk assessment is often defined as an event occurring in a specific place and at a specific time. In cumulative risk assessment, the focus is on the population of concern, so that all relevant exposures are to be included. The exposure event then might encompass several locations over a broad and varied time period. These temporal and spatial aspects of cumulative risk analyses might then require additional consideration as the dose-response data are integrated in the risk characterization.

5.4.2. Dose-response Data. When determining groups of chemicals (as shown in Figure 4-6b), the evaluation of component data includes steps that require consideration of target organ specific data. Toxicity databases, such as the U.S. EPA IRIS database, may provide toxicologic information only on a single critical effect (i.e., that effect occurring at the lowest exposure level). Additional data such as those in the U.S. EPA HEAST documents, ATSDR toxicological profiles and interaction profiles, or those obtained from primary literature searches may be needed to identify additional effects and target organs. Whether adequate dose-response data are available affects the

grouping of chemicals and also the potential for estimating the joint toxicity of the chemical combinations. When information on secondary effects is inadequate, the risk characterization should address the impact of this uncertainty, particularly regarding joint toxicity that may be underestimated for those secondary effects.

5.4.3. Multiplicity Issues with Exposures or Effects. The characterization of complex exposures, even to a single chemical, might include well measured exposures along with those that are conjectural or poorly understood. For example, concern might exist for consequences of natural disasters (lightning induced fires, flooding) or mechanical malfunction (e.g., intermittent emissions from an aging incinerator), neither of which may have occurred at the site being assessed. One option is to present the combined exposures and risks numerically for those aspects that can be quantified and then describe the complete exposure and risks in qualitative terms, estimating the impact on the risk estimate of the missing factors. In these situations, the analyst should identify the source of the uncertainty, the available information to address it, and the assumptions invoked in the risk analysis to compensate for the missing information.

5.4.4. Decision Steps in the Assessment Process. Throughout the analysis, decisions will be made that influence the final conclusions of the assessment. Such decisions may occur during planning and scoping and during the iterative analysis. These decisions include the following:

- the goal of the assessment
- the spatial and temporal scope and scale of the analysis
- the agents retained for analysis
- the exposure scenarios considered

- the populations considered and
- the choice of methods for evaluating risks posed under the selected exposure scenarios.

The criteria used to make each of these decisions need to be clearly identified and consistently applied. Although the criteria for planning, scoping, and problem formulation are often determined early in the assessment process in consultation with the stakeholders, these criteria must be clearly described in the risk characterization to ensure transparency and clarity of the assessment's conclusions. When possible, a sensitivity analysis should be performed to determine the relative impact of these decisions on the resulting risk estimates. For example, if an exposure pathway is screened out of the scope because the stakeholders desire focus on aspects under local control, or because of the unlikelihood of obtaining adequate data for that pathway, then the influence of ignoring that pathway should be described in the risk characterization, even if merely to identify the direction of potential error (i.e., to underestimate or overestimate the risk).

One approach to the evaluation of the decisions made during the assessment is to determine the usefulness of the results, both in terms of addressing the issues laid out in the scope, as well as providing information relevant to decisions about the available remediation options (Figure 5-2). Suggested steps to follow when determining the usefulness of the results include the following:

- Evaluate compatibility of exposure, population, toxicity information.
  - extrapolations (animal species, exposure route or duration, joint toxicity, population susceptibility)
  - measurement units (exposure or dose, toxic effects)
  - omissions (pathways, chemicals, subpopulations, toxic effects)

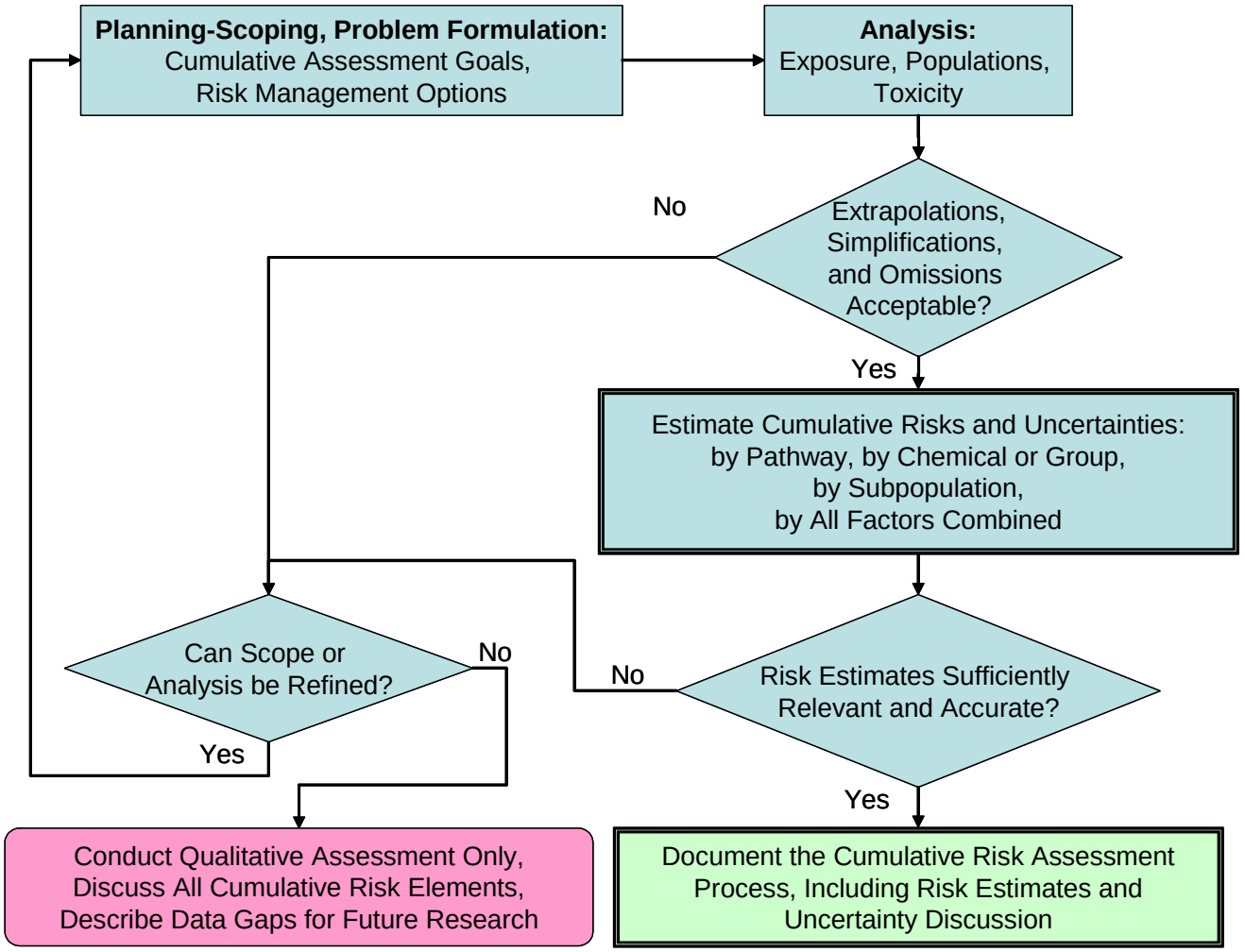


FIGURE 5-2

Risk Characterization Decisions. Iteration to revisit the scope and analysis steps might resolve apparent incompatibilities between the results and the available remediation options. Otherwise, a qualitative cumulative risk assessment might be indicated.

- Evaluate health risk estimates and uncertainties.
    - by subpopulation
    - by pathway
    - by chemical or chemical group
    - for all factors combined.
- Evaluate relevance and accuracy of risk estimates with respect to goals and risk management alternatives identified in planning and scoping phase.
- Identify next steps.
    - revise analysis methods and seek new research information
    - revisit planning and scoping steps
    - consider qualitative assessment, including cumulative risk issues and identification of needed data for cumulative risk.

5.5. SUMMARY RECOMMENDATIONS

5.5.1. Combined Characterization of Health Risk. Among the results in the cumulative risk characterization should be the following:

- Risk description for the main population of concern. The risks must address those identified in the problem formulation phase as well as all major exposure pathways and toxic effect groups.

- Risk description for the high end risk groups or population subgroups. These high end groups should reflect those with high single chemical exposures as well as those with high exposure to interactive chemical combinations. Subgroups of concern include those that are inherently sensitive because of biological characteristics and those that are of increased risk because of the cumulative aspects of risk, namely toxicologic interactions. Such sensitivity might be related to physiologic characteristics or exposure factors that could enhance the synergistic activity of one or more chemicals. This latter group is unique to cumulative risk assessment.

- Summary of key uncertainties and suggestions for improvement.

5.5.2. Interpretation of Results in Context of the Formulated Problem. Results should highlight those risk estimates that address the issues identified in the problem formulation step according to the consensus details of the planning and scoping step. (See planning and scoping documents referred to in Chapter 1 for details.) The risk assessment should contribute useful information to the risk management decisions. In particular, the uncertainties should be linked to the stakeholder concerns and interpreted in the context of the risk management options as well as the risk estimates themselves. If the results do not seem to be compatible with the scope or are not sufficiently accurate or detailed to be useful to the risk management decisions, then the scoping and problem formulation steps should be revisited. For example, if the primary concern is risks caused by contamination at the site, then a comparison is needed with risks from exposures to background or off-site contamination.

5.5.3. Summary. The outcome of the risk characterization should provide a useful integration of the data needed by the risk manager to make decisions regarding a cumulative risk trigger. Results of the analysis may aid the risk manager in deciding the extent of potential health risks from population, exposures and whether remedial action is necessary. A cumulative risk characterization may include sensitive information such as the number of people exposed, risk estimates for health endpoints of concern to the community, uncertainties regarding the exposure and health risk estimates, and bottom-line conclusions in support of a regulatory decision. Thus, results of the risk characterization must be communicated clearly, with important issues and uncertainties highlighted. Finally, the identification of data gaps, chemicals placed on a watch list, and research needs that may improve the risk characterization should be articulated.

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7. GLOSSARY

Significant terms used in this guidance document and in cumulative health risk assessments are defined below. Definitions have been extended to include the implications for cumulative risk assessment. Many general risk terms are not included because standard definitions are readily available elsewhere. In particular, EPA and ATSDR have developed extensive glossaries of risk assessment terms (available at http://www.epa.gov/iris/gloss8.htm, http://oaspub.epa.gov/trs/ and http://www.atsdr.cdc.gov/glossary.html).

Absorbed dose. The concentration of a chemical inside the body, upon being taken in through an absorption barrier, e.g., skin absorption, ingestion (see *dose*).

Acute toxicity. Adverse effect expressed within a short time (generally from minutes to a day) following exposure to an agent (here, chemical). Most experimental acute toxicity studies involve response to a single, large dose of an agent, although occasionally to multiple exposures given within a short time period. EPA defines acute exposure to be 24 hours or less.

Additivity. Concept that cumulative or joint risk can be represented by adding the component information, commonly used for chemical doses or their toxic responses. Additivity is the default assumption for evaluating health effects of multiple chemicals. Specifically, an additive formula for the toxicity of multiple chemicals is some function of a linear combination of the component exposures or toxic responses (such as a weighted sum). Exposure can be represented by the external exposure level or the internal dose, and toxic response can be represented by the frequency or probability of toxicity or the measure of toxic effect. (The terms *exposure* and *effect* must be explicitly defined for *additivity* to be meaningful for a given combination of chemicals.)

Agent. An environmental chemical that could cause harm to human health. (More broadly interpreted, this term can include biological stressors such as anthrax and physical stressors such as noise and heat as well as stressors causing impacts other than toxicity. This guidance focuses on chemicals and human health effects.)

Aggregate exposure. The combined exposure of a receptor (individual or population) to a single chemical. The chemical can originate from multiple sources and be present in multiple media, and exposures can occur by different routes and over different time periods. Under current Agency definitions, aggregate exposure does not translate to cumulative risk because it addresses only one chemical; however, combining aggregate exposures by addressing two or more chemicals would constitute a cumulative risk assessment.

Antagonism. The process by which two or more chemicals together exert an effect that is lower than would be predicted by simple addition, which is usually defined as adding the doses or responses of the individual chemicals. For example, copper has

been shown to protect against cadmium poisoning. Thus, depending on their levels (compared with those at which this sparing effect is observed), ingesting both could reduce the combined toxic response predicted from summing the individual responses. Additivity must be clearly defined (e.g., dose or response addition) to appropriately assess whether antagonism exists, and care must be taken to understand the dose-response relationships. For example, if dose addition were applied when in fact the chemicals were toxicologically independent (meaning response addition should be applied), then the result would be lower than expected and could be misinterpreted as antagonism.

Bioactivation. Process by which a chemical or its metabolite is biochemically converted to a reactive intermediate. For example, chloroform is converted in the body to the reactive intermediate phosgene (which was historically used as a chemical weapon). In a mixture, one chemical can trigger the toxic effects of another by affecting its bioactivation.

Biomolecule. Any molecule synthesized by an organism, e.g., an enzyme or other protein.

Chemical antagonism. The process by which two or more chemicals undergo a chemical reaction to produce a different chemical, which has a lower toxic effect than that predicted from adding the toxic responses of the original chemicals; this toxic effect might also qualitatively differ from those of the original chemicals (see *antagonism*).

Chemical exposure class. A group of chemicals that are physically and chemically similar, primarily in chemical structure and potential for environmental transformation and transport (as directly linked to potential exposure). For example, chlorinated ethanes are considered a chemical exposure class because they are generated by the same commercial process and have similar fate and transport characteristics so are often found together in the environment.

Chemical mixture. Two or more chemicals that coexist (e.g., whether at a generating source, dispersed in the environment, or inside a person) and could contribute to combined toxicity; their actual identities or origins might or might not be known. Examples include: (1) Aroclor 1254 (a commercial combination of PCB congeners) in soil and (2) benzene and ethanol together in the body due to workplace exposures to benzene followed by drinking beer at home. In parallel with the common risk assessment term for single chemicals, this can also be referred to as the “mixture of concern” (see *whole mixture* and *complex mixture*).

Chemical synergism. The process by which two or more chemicals undergo a chemical reaction to produce a different chemical, which has a greater toxic effect than that predicted from adding the toxic responses of the original chemicals; this toxic effect might also qualitatively differ from those of the original chemicals (see *synergism*).

Chemical toxicity class. A group of chemicals that are toxicologically similar, primarily due to similarities in chemical structure and biologic activity. Such a group with similar toxicities could also be a chemical exposure class, e.g., if they were produced by the same commercial process and frequently coexist in the environment. Where the composition of such a group is well controlled (e.g., by a standard generating process), the mixture could be evaluated as a single chemical. Examples include dioxins, coplanar (dioxin-like) polychlorinated biphenyls (PCBs), and ketones; these similar groups of compounds can also interact toxicologically with chemicals outside their class.

Complex interaction. The interaction produced by three or more chemicals acting together that cannot be described according to other interaction definitions. (For two chemicals, see *pair-wise interaction*.)

Complex mixture. A mixture containing so many chemicals that any estimate of its toxicity based on the toxicities of its components is too uncertain to be useful. The chemical composition of this type of mixture could vary over time or with different generating conditions. The various components of complex mixtures can be produced as commercial products or they can be generated simultaneously as byproducts of a process (e.g., diesel exhaust emissions), or they can coexist because of disposal practices. To assess risks for complex mixtures, exposure and toxicity data for the complete mixture are preferred (see *whole mixture method*).

Component(s). Single chemicals that make up a mixture. These could be further classified by the type of toxicity they cause. For example, the individual toxicities of dichloroethylene and acetone ingested together could be separately assessed, as well as their potential for toxicologic interaction.

Component-based method. An approach for evaluating a mixture using exposure and dose-response information for the individual chemicals in that mixture. This approach is useful for comparing mixtures that contain the same chemicals but in differing concentrations and proportions to determine whether they are similar mixtures. (See *whole mixture method* for comparison.)

Contact. The connection between a receptor (person) and a chemical (e.g., in soil, water, or air). Contact can be continuous (constant) or intermittent (e.g., only occurring at discrete times during a day or season).

Critical effect. The toxic effect characterized by the lowest observed adverse effect level (LOAEL), which represents the lowest dose at which any adverse effect is observed regardless of its nature (e.g., severity) and serves as the basis of the toxicity values used to assess noncancer effects (see *reference dose*, *reference concentration*, and *toxicity value*).

Cumulative risk. The combined risk to a receptor (individual or population) from exposures to multiple agents (here, chemicals) that can come from many sources and exist in different media, and to which multiple exposures can be incurred over time to

produce multiple effects. (Health risks are the focus of this guidance.) More than one chemical must be involved for the risk to be considered cumulative.

Detoxify. Diminish or remove the toxicologic effect of a chemical, e.g., by metabolic or chemical reaction with another (sometimes referred to as *detoxicate*).

Dose. The amount of a chemical that enters into the body (from being administered, taken, or absorbed), usually expressed as milligrams of substance per kilogram of body weight. If the exposure surface crossed is an absorption barrier, the dose is an absorbed dose/uptake dose; otherwise it is an intake dose. The dose represents the amount available for interaction, e.g., with other chemicals, metabolic processes or biologically significant receptors.

Dose addition. The process by which the doses of individual chemicals in a mixture are summed to represent an overall mixture dose. This approach assumes that the chemicals are toxicologically similar, with each behaving as a concentration or dilution of an index chemical in that mixture (effectively as a senior or junior clone). The mixture dose is estimated by summing equivalent doses of the individual chemicals, which are determined by scaling the toxic potency of each to that of the index chemical (see *index chemical* and *hazard index*).

Effect. The health endpoint resulting from the chemical exposure(s), which can be estimated or observed (such as increased liver enzyme levels, cardiac arrhythmia, or cancer). Human health effects are typically estimated from effects observed in animal toxicity studies, with various adjustment factors applied as appropriate.

Endpoint. An observable or measurable biological event; this can be an observed effect or a chemical concentration (e.g., of a metabolite in a target tissue) used as an index of an exposure.

Exposure. The contact between a chemical and the outer boundary of an organism, quantified as the amount available at the exchange boundaries (e.g., skin, lungs, or gut). This contact can be intermittent or continuous. The total amount of exposure is determined by multiplying the exposure time, frequency, and duration.

Exposure duration. The total length of time over which an exposure occurs, given in years for chronic exposures. Unless time-weighted averaging can be justified, repeated exposures should consider duration to be the time period from start to end of the exposure. For example, if an individual contacts a chemical 10 minutes a day for 350 days a year over 8 years, the exposure duration is 8 years.

Exposure frequency. How often a receptor is exposed to a chemical over a year, for chronic exposures. For example, if an individual contacts a chemical 10 minutes a day for 350 days a year over 8 years, the exposure frequency is 350 days/year.

Exposure pathway. The physical course a chemical takes from its source to a receptor. If an exposure is occurring the exposure pathway is considered complete. The elements of a complete pathway are (1) a chemical source (e.g., waste lagoon) and mechanism of release (e.g., volatilization or leaching); (2) contaminant fate (such as physical or chemical changes) and transport through the environment (e.g., air, water, and soil); (3) an exposure point, or the location where the receptor comes in contact with either the source itself or a medium carrying the chemical; and (4) an exposure route.

Exposure route. The way a chemical gets inside an individual who comes in contact with it, e.g., inhalation, ingestion, or dermal absorption.

Exposure time. How long a receptor is in intermittent or continuous contact with a chemical over a day. For example, if an individual is in contact 10 minutes a day for 350 days a year over 8 years, the exposure time is 10 minutes/day.

Extrapolation. The process by which information is inferred to fill a gap in existing data. Commonly used to estimate the response at a low dose, often well below the range of the experimental data, or equitoxic doses across species. The better approaches use biologically based mathematical models.

Hazard identification. The process of determining whether exposure to a given chemical or mixture could cause harm (adverse health effects). It can also involve qualitatively indicating the nature of the likely health effects.

Index chemical. The one chemical in a mixture against which the toxicities of the other chemicals are normalized so equivalent doses can be calculated and summed to represent the total dose of the mixture. Two key criteria are used to select an index chemical: first, good toxicity data should exist (with a clearly defined dose-response relationship), and second, it should represent the whole group well. To illustrate, 2,3,7,8-TCDD is the index chemical for dioxins because it has the best toxicity data and is considered a good representative of this group of compounds; the concentrations of the other dioxins are multiplied by their individual potencies relative to this isomer, then summed as “2,3,7,8-TCDD equivalents” to arrive at the dose for the dioxin mixture.

Induction. The initiation or elicitation of a certain response, which can be beneficial or adverse. The response can be evaluated across a wide scale, from the genetic and cellular level to the tissue and whole-organism level. For example, at the genetic level the activity of a regulatory protein can induce increased expression of a certain gene, while at the molecular level the binding of a chemical to a biomolecule can induce an enzyme to increase its reaction rate or initiate a series of biochemical reactions that can ultimately result in an adverse health effect (such as kidney hyperplasia).

Inhibition. The process by which a chemical that is not itself toxic acts on another chemical that is toxic and makes that chemical less toxic. (More broadly, this term means the limitation or prevention of a certain response, which could be beneficial or

adverse. For example, if the response is cell growth, one toxic chemical might inhibit the growth of certain cells needed for a system to function properly, while another might inhibit cell proliferation that would otherwise lead to tumor formation [e.g., a chemotherapeutic agent]. For mixtures, this term is often used to describe beneficial inhibition as indicated above.)

Interaction. Generally, the influence or action of one chemical on the behavior or effect of another, which can be mutual or reciprocal. In the environment, interactions among chemicals can alter their physicochemical forms and transport characteristics (e.g., increasing or decreasing mobility and bioavailability). Within the body, one chemical can interact with another (or others) to cause toxicity, increase or decrease a response, or completely change the response expected from the individual chemicals acting alone. Both pharmacokinetics and pharmacodynamics could be altered by the interactions of chemicals that can target different organs or organ functions and can result from simultaneous or sequential exposures (so long as they are present at the same time within the body, e.g., due to pharmacokinetic overlap). The Agency has defined toxic interactions as being less or more than additive.

Interindividual variability. Differences among individuals within the same species, e.g., differential susceptibility of humans to a given heath effect from exposure to a given hazard, which can result from metabolic or other pharmacokinetic differences. To illustrate for a physical hazard (ultraviolet radiation), one person might sunburn after spending an hour outside, while another might not burn for several more hours, i.e., until the exposure is much greater. Similar variability exists for exposures to chemicals and within other species (see *intraspecies variability*).

Internal dose. The dose of a chemical inside the body. Depending on the nature of the data, this can be expressed as (1) the total absorbed dose of the original chemical (also referred to as the parent compound), (2) the concentration of the parent compound in target tissues, (3) the total amount of the toxicologically active metabolite, or (4) the concentration of the toxicologically active chemical species in the target tissues.

Interspecies variability. Differences between different species (e.g., between rats and mice, or between rats and humans). A factor of 10 is often applied to account for these differences in deriving a standard toxicity value to estimate human health effects from animal studies, as indicated by the appropriate scientific data.

Intraspecies variability. Differences within a single species (e.g., among rats or among mice, but not between rats and mice). A factor of 10 is often applied to account for these differences in deriving a standard toxicity value to estimate human health effects as indicated by the appropriate scientific data (see *interindividual variability*).

Joint toxicity. The toxic outcome resulting from the interaction of a set of two or more chemicals. This outcome can be lower than, equal to, or greater than that predicted by adding the doses or responses of the component chemicals acting alone.

No observed interaction. The negative outcome of a study of two or more chemicals, which indicates that they do not interact at the levels studied, to alter either behavior or effect. For example, considering toxic interactions, if two chemicals were administered together or coexist within the body due to pharmacokinetic overlap (when exposure timing differs), and if the effect produced does not differ from that expected by the two chemicals acting alone (which could also be no effect), then no interaction would be observed. (Note: this term was used to categorize study outcomes for EPA's Mixtox data base.)

Parent compound. The original form of a chemical prior to its transformation in the environment (e.g., by photolysis or microbial degradation) or its transformation within the body (e.g., by metabolism).

Pharmacodynamics (PD). The study of the biochemical and physiological effects of drugs and their mechanisms of action, or what they do to the body (see *toxicodynamics* for the parallel study of toxic chemicals).

Pharmacokinetics (PK). The study of the absorption, distribution, metabolism, and excretion of a drug in and from the body (see *toxicodynamics* for the parallel study of toxic chemicals).

Physiologically based pharmacokinetic (PBPK) model. A mathematical model that estimates the dose to a target tissue or organ by taking into account the rates of absorption into the body, distribution among organs and systems, metabolism, and elimination. It typically takes the form of compartments that represent organs and tissues, linked by flow (e.g., blood) exchanges, with associated weights, volumes, flow rates and fractions, partition coefficients, and metabolic constants based on physiological studies. These mechanistic PBPK models translate exposure to tissue concentrations, characterizing tissue dosimetry for different species, doses, and route extrapolations. (Although PBPK models can offer insights into metabolic interactions for mixtures, integrating multiple contaminants greatly increases the amount of data needed for parameter estimates.)

Potentiation. The process by which a chemical that is not itself toxic acts on another chemical that is toxic and makes that chemical more toxic. (More broadly, this term means the enhancement of a certain response, which could be beneficial or adverse. For mixtures, this term is often used to describe an enhanced adverse response, as indicated above.)

Receptor. The individual or population group actually or potentially exposed to a chemical (receptors can be real or hypothetical). For contaminated sites, various receptors are typically hypothesized to evaluate potential risks under likely future uses, to help guide risk management decisions. In cases where real people might be incurring exposures (e.g., including cleanup workers), these should clearly be assessed.

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

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

Reference value (RfV). An estimate of an exposure for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime. It is derived from a BMDL, a NOAEL, a LOAEL, or another suitable point of departure, with uncertainty/variability factors applied to reflect limitations of the data used. [Durations include acute, short-term, subchronic, and chronic and are defined individually in this glossary.] [Reference value is a term proposed in the report *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002e), and is a generic term not specific to a given route of exposure. U.S. EPA develops numerical toxicity values for the RfD and RfC only; no numerical toxicity values are developed for the RfV.]

Response addition. The process by which the toxic response of each chemical in a mixture is summed to represent an overall mixture response. This approach assumes the chemicals are toxicologically independent, and the toxic response can be defined as a rate, incidence, risk, or probability of effect. For mixtures, the response equals the conditional sum of the toxic responses for individual chemicals as defined by the formula for the sum of independent event probabilities. For two-chemical mixtures, this means the incremental toxic effect from exposure to the first chemical is the same whether the second chemical is present or not. (Response addition underlies the standard process for estimating combined cancer risks by summing the cancer risks of individual chemicals.)

Risk. The probability (for carcinogens) or potential (for noncarcinogens) that adverse health effects to result from chemical exposures (see *cumulative risk*). (More broadly, this term also covers other types of risks and other stressors, but the focus of this guidance is the potential for harm to human health from exposures to multiple chemicals.)

Similar components. Single chemicals that cause or are expected to cause the same type biologic activity based on toxicity studies or chemical structure (e.g., as analogues, reflecting the structure-activity relationship). In addition to similar characteristics in terms of physiological processes and toxicity within the body, these chemicals would

also be considered to have similar fate and transport characteristics in the environment. Evidence of toxic similarity can include (1) similarly shaped dose-response curves, (2) parallel log-probit or logit dose-response curves for quantal (presence-absence) data on the number of animals (or people) exhibiting a specific response, and (3) the same mechanism of action or toxic endpoint. Trichloroethylene and tetrachloroethylene are examples of similar components.

Similar mixtures. Mixtures of similar chemicals although they might differ slightly from one another (e.g., same chemicals but in slightly different proportions or the same chemicals in nearly the same proportions but missing a few or have a few new ones). Similar mixtures cause or are expected to cause the same type of biologic activity, and they would act by the same modes of action or affect the same toxic endpoints. In addition to similar characteristics in terms of physiological processes and toxicity within the body, these chemicals would also be considered to have similar fate and transport characteristics in the environment. Varying grades of gasoline (e.g., from regular to super-premium) are examples of similar mixtures.

Simple mixture. A set of chemicals that is small enough for each individual chemical to be identified, so the toxicity of the mixture can be characterized by combining the toxicities and considering the interactions of the component chemicals. For example, acetone, methylene chloride, and ethanol present together in water to which someone could be exposed would comprise a simple mixture.

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

Source. The location of the environmental chemical(s) being assessed (e.g., an incinerator stack or waste lagoon), from which it is released and can subsequently be transported through the environment.

Stressor. A chemical that could cause harm. More broadly, this term also covers biological agents such as anthrax and physical agents such as noise and heat. The umbrella definition provided in the *Framework for Cumulative Risk* (U.S. EPA, 2003a) extends to any physical, chemical, or biological agent that can induce an adverse response, e.g., a chemical, noise, loss of habitat, or lack of food or water.

Substrate. The substance to which another material attaches or upon which it acts, for example an environmental chemical or biomolecule upon which an enzyme acts. This can be a chemical that binds to the active site of an enzyme or other protein in the body.

Synergism. The process by which two or more chemicals together exert an effect that is greater than would be predicted by simple addition, which is usually defined as adding the doses or responses of individual components. For example, depending on

their levels (compared with those at which the toxic interaction is observed), inhaling both carbon tetrachloride and acetone could produce a more toxic liver response than would be predicted from summing the individual responses. Additivity must be clearly defined (e.g., dose or response addition) to appropriately assess whether synergism exists; care must be taken to understand the dose-response relationships. For example, if response addition were applied when in fact the chemicals were dose-additive, then the result would be higher than expected and could be misinterpreted as synergism.

Target Organ. The biological organ adversely affected by a given chemical or mixture.

Toxicity value. The standard value used to translate chemical exposures (doses) to estimates of cancer risks or the potential for noncarcinogenic effects. The cancer or noncancer toxicity value is specific to the chemical (or mixture), route of exposure, and duration over which the exposure occurs. These values are typically derived from animal studies, with adjustment factors applied to develop estimates for humans. For the cancer endpoint the toxicity value is termed the slope factor, and for noncarcinogens it is termed the reference concentration (RfC) for inhalation exposure and reference dose (RfD) for oral exposure.

Toxicodynamics (TD). The sequence of events at the cellular and molecular levels leading to a toxic response following exposure to a chemical. This involves the processes underlying the effect severity, reversibility, recovery, and adaptive response. (See the general term *pharmacodynamics*, which was developed for drug studies. Although the TD term is often used in risk assessments of environmental chemicals, pharmacodynamics could be a more appropriate term for certain chemicals, e.g., essential metals, depending on the exposure levels.)

Toxicokinetics (TK). The characterization and quantification of the time course of absorption, distribution, and metabolism (or biotransformation) in the body and elimination (or excretion) from the body of a chemical taken in. (See the general term *pharmacokinetics*, which was developed for drug studies. Although the TK term is often used in risk assessments of environmental chemicals, pharmacokinetics could be a more appropriate term for certain chemicals, e.g., essential metals, depending on the exposure levels.)

Toxicologic interaction class. A group of chemicals that are toxicologically similar in terms of the direction of toxicologic interaction (synergism, antagonism, or additivity). For any given interacting chemical, when paired with other members of this group the direction of the interaction would be the same. This group can be defined as a toxicologic interaction class only for specific toxic endpoints. Ketones and selenium compounds are examples of interaction classes.

Trigger. A condition involving more than one chemical that catalyzes a cumulative risk study, such as (1) multiple sources/releases, (2) measured or inferred chemical concentrations, or (3) illness in a given population.

Unable to assess. The effect of the chemical (mixture) cannot be classified, for example due to lack of proper control groups; lack of statistical significance; or poor, inconsistent, or inconclusive data in the available toxicity studies.

Uncertainty factor (UF). An adjustment factor applied to experimental data in deriving toxicity values used to estimate health risks and the potential for noncancer effects. These factors are applied to account for (1) variation in susceptibility among members of the human population; (2) uncertainty in extrapolating animal data to humans; (3) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure; (4) uncertainty in extrapolating from a lowest-observed-adverse-effect level (LOAEL) instead of a no-observed-adverse-effect level (NOAEL); and (5) uncertainty associated with extrapolation when the database is incomplete (which might be addressed by a modifying factor).

Whole mixture. A mixture that is evaluated in its entirety, usually with exposure levels for the entire mixture unadjusted for any differences among the toxic potencies of its component chemicals. Some whole mixtures can be defined and are reproducible, e.g., where the process that created them is well understood. Other whole mixtures are defined by groups of structurally similar chemicals that often co-occur. Examples include total chromium and compounds and total petroleum (hydrocarbons). This term is often applied to highly complex mixtures with components that cannot be fully identified or reproducibly measured. Diesel exhaust, gasoline, and toxaphene are specific examples.

Whole mixture method. An approach in which the whole mixture is treated as a single entity, similar to the way single chemicals are assessed, and thus requires dose-response information for the whole mixture. This approach is used for complex mixtures, and it is best applied to mixtures with a composition that is constant over the entire exposure period. It differs from the component-based method because the toxicity information inherently reflects unidentified chemicals in the mixture as well as any interactions that might be occurring among the chemicals. (See the *component-based method* for comparison.)

APPENDIX A
CUMULATIVE RISK TOOLBOX

This appendix identifies resources that can be used to address various elements of cumulative risk assessments for specific situations and contaminated sites. Several have been applied at sites being addressed by the U.S. Environmental Protection Agency (U.S. EPA) and U.S. Department of Energy (DOE). Many of these resources are also useful for other types of cumulative risk analyses, and tools from U.S. EPA studies for several regulatory programs are also included here.

Many federal, state, academic, and professional organizations have developed general risk assessment guidelines and tools for a variety of situations. While some resources clearly consider multiple exposures to multiple chemicals, such as the standard *Risk Assessment Guidance for Superfund* (U.S. EPA, 1989a), relatively few are described as explicitly assessing cumulative risks by specifically addressing groupings or joint toxicity, or by being population focused. The main body of this report includes discussions of how more recent cumulative risk approaches can enhance the traditional risk assessment approach. The toolbox of information resources presented in this appendix includes many tools developed for general risk assessments that can also be used or adapted for population specific cumulative risk assessments, or whose underlying approaches offer insights for these assessments. This toolbox is not intended to be comprehensive; the aim is simply to highlight those resources that could be useful for cumulative health risk assessments. This appendix focuses on chronic exposures, but some resources related to acute or subchronic exposures (such as those developed for health and safety in the workplace) are also included.

Resources that support planning, scoping, and problem formulation, including stakeholder involvement, are identified in Section A.1. Those that support evaluations of contaminant fate and transport and exposure, which range from summary data on physicochemical constants to specific transport and exposure models, are highlighted in Section A.2. Resources that support the toxicity evaluation are offered in Section A.3, and those that support the characterization of risk and uncertainty and presentation of results are highlighted in Section A.4. Several resources cover more than one of these topics; where this is the case, they are generally listed within their main area of emphasis. The information reproduced here is believed accurate as of the publication date. The intent is to post these resources on U.S. EPA's Web site and update them regularly.

A.1. RESOURCES FOR PLANNING, SCOPING, AND PROBLEM FORMULATION

Topics addressed during iterative planning, scoping, and problem formulation include the purpose and scope of the assessment (which involves considering multiple chemicals, exposures, effects, and population groups), the products needed, the data to be collected and synthesized, the general assessment approach, and stakeholder involvement. Cumulative risk assessments are complex because of the very large number of potential combinations of chemicals and interactions inherent to environmental settings.

During this initial and iterative phase of a cumulative assessment, a main focus is on which chemicals present are most likely to interact and what the nature of those interactions might be. The internet has emerged as a very valuable tool for stakeholder involvement. It can be used to easily provide information about the project and

associated scientific issues for a wide audience, which can be browsed on-line or downloaded at the user's convenience. It can also be used to notify interested parties of upcoming meetings or the availability of specific reports for the site. Project websites and e-mails can also be used to effectively solicit and receive stakeholder inputs about the project. Limited-access web sites can be also used to share and evaluate draft information as it is developed.

The usefulness of internet-based approaches for stakeholder involvement is described further below, and examples of specific tools are included in Table A-1. (Note that most resources presented in this toolbox are available through the internet.)

1. *Low cost to involve many stakeholders.* Although fixed costs to build a website can be somewhat high, the marginal cost to involve additional stakeholders is nearly zero, so the internet can be cost-effective for projects with extensive stakeholder participation. For example, a document can be posted on a website very cheaply; in contrast, mailing would require postage, printing, and paper costs with marginal costs that do not diminish significantly with additional users (essentially free via the internet method). Receiving stakeholder inputs through the web or e-mail can also save costs compared with paper-based approaches.

2. *Wide geographical reach.* Using a website and e-mail allows ready access to information and opportunity for participation regardless of stakeholder location, in contrast to traditional methods that typically focus on people nearby. This is particularly important when travel to public meetings is restricted (e.g., due to cost, schedule, or physical disabilities). This broad accessibility can increase participation because additional people become aware of the project (e.g., through web searches). The use of e-mail can also be effective because information can be delivered to a broad set of stakeholders at their desktops.

3. *Availability.* Information posted to a public website is available 24 hours a day, 7 days a week, and can be accessed at times convenient to the user – which can also increase participation. (People without computers could access the internet from libraries or other such facilities during regular hours.) Likewise, e-mails can be opened at the user's convenience.

4. *Extent of information.* Large amounts of data and other information can be provided via the internet, much more than would be reasonable by other means (meetings and paper). Further, this information can be reviewed at whatever level of detail and pace the user prefers.

5. *Immediacy.* Information can be made available essentially immediately via the internet. This can be especially useful for situations that might arise when the level of concern is high (e.g., when wildfires or accidents cause acute releases).

6. *Data interactivity.* Websites can integrate the capabilities of many different databases, geographic information systems (GISs), graphing, and other tools so stakeholders can play with data and information in ways that would not be possible under traditional methods (e.g., with hard copies). This can include "clicking" on specific locations to identify multiple chemicals present there, or searching to find all locations with a specific combination of chemicals (e.g., which could be known to interact).

7. *Flexibility.* Information shared vie the web or e-mail can be made available in different types of electronic formats, which can facilitate use by multiple parties. Also, websites and e-mail communications can be readily adapted to accommodate new types of information as it is developed.

Selected resources that can be used to support planning, scoping, and problem formulation for cumulative risk assessments, including stakeholder involvement, are briefly described below. Selected information is also summarized in Table A-1 at the end of this section.

- **Framework for Cumulative Risk Assessment (U.S. EPA).** The framework document released in spring 2003 identifies an umbrella structure for cumulative risk assessments, identifies key issues, and defines common terms. It summarizes basic elements of the cumulative risk assessment process and presents a flexible structure for conducting cumulative risk assessments. Neither a procedural guide nor a regulatory requirement, this framework is expected to evolve over time. The document does not present protocols to address specific risk issues; rather it provides good information about important aspects of cumulative risk (U.S. EPA, 2003a). A main foundation of this guidance, the report is available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=54944.

- **Planning and Scoping for Cumulative Risk Assessment (U.S. EPA)**. Guidance was published in 1997 by the U.S. EPA Office of Science Policy, Science Policy Council, which reflects the Agency's policy statement for planning and scoping for cumulative risk assessments (U.S. EPA, 1997a). This guidance presents ideas for broad-based approaches, including consideration of multiple endpoints, sources, pathways and routes of exposure; community-based decision making; flexibility in achieving goals; case-specific responses; a focus on all environmental media; and holistic reduction of risk. This report is available at http://www.epa.gov/OSA/spc/2cumrisk.htm. Lessons learned from cumulative

risk case studies are captured in a companion technical memorandum (report) (U.S. EPA, 2002f), available at http://www.epa.gov/osp/spc/llmemo.htm.

- **Environmental Justice Geographic Assessment Tool (U.S. EPA) and Similar Ranking/Prioritization Tools**. Designed jointly by the U.S. EPA Office of Environmental Information and Office of Environmental Justice, this tool is a GIS-based module to support front-end scoping of cumulative assessments. It combines environmental, socioeconomic, and health indicators in statistical tables, and it was initially developed to evaluate potential issues related to environmental justice. Where a community-based approach is applied, this tool can be helpful in identifying the risk problems to be assessed. (Although presented here within the planning/problem formulation stage, this can also be a used to support risk characterization.)

- **Site Conceptual Exposure Model (SCEM) Builder (DOE).** The SCEM Builder was developed by the DOE Office of Environmental Policy and Guidance in 1997 to support planning, scoping, and problem formulation for risk assessments at contaminated sites, by providing a tool to build SCEMs. An SCEM is a visual representation of scenarios that organizes information about sources of contamination, release mechanisms, exposure pathways, and receptors for a site and can be used to address data gaps. These conceptual models are often used to develop data quality objectives (DQOs) and prioritize field sampling activities, in order to help reduce uncertainty associated with risk characterization. Using this tool, assessors can build SCEMs for a given site and modify variables to refine the model, e.g., to reflect stakeholder inputs. This tool can also be used to develop SCEMs for various "what-if" scenarios to help bound data uncertainties. It is available at http://tis.eh.doe.gov/oepa/programs/scem.cfm.

- **Stakeholder Involvement (U.S. EPA, DOE).** Several resources exist that document the procedures and approaches implemented to support stakeholder involvement activities in risk assessment projects. These range from national policy guidance documents to site-specific reports that chronicle the approaches taken by individual projects to solicit input from stakeholders and incorporate their concerns and ideas into the analysis plan. Guidance from the U.S. EPA Superfund and Environmental Justice programs (captured in Table A-1) encourages community involvement and can be useful for cumulative risk assessments at contaminated sites.

  A number of stakeholder involvement examples exist that can offer insights for cumulative risk assessment projects. Many are available for contaminated DOE sites, where citizen advisory boards have been established to provide input during planning and scoping and as assessments progress. The mission or charter language prepared by these advisory boards can offer clues for other projects. Such language typically includes general "rules of engagement" (including respect for diverse opinions) as well as specific roles and

responsibilities (notably with regard to providing advice and recommendations instead of making management decisions for the project).

For example, a citizen's advisory board (CAB) was created to facilitate public outreach for the DOE Savannah River Site. That CAB consists of 25 individuals from South Carolina and Georgia chosen by an independent panel of citizens from approximately 250 applicants that reflect the cultural diversity of the local population. The CAB has considered itself a major component of the risk assessment/management team for the site and maintains a website (www.srs.gov/general/outreach/srs-cab) that offers ideas that can be useful for similar programs at other sites.

A stakeholder advisory board has also been established at the DOE Hanford site in Washington. Information on the Hanford Advisory Board (HAB) is available at http://www.hanford.gov/public/boards/hab/. This Board created a calendar for public involvement that lists upcoming meetings and other events at which input from affected parties and stakeholders is encouraged. Nearly a decade ago, an advisory group that included many stakeholders and a technical expert team from the project considered an approach for a comprehensive impact assessment for the Columbia River that flows next to the site; that effort is no longer underway as defined at that time, but related information can be found on the internet (e.g., see http://www.hanford.gov/docs/rl-96-16/). The DOE management at Hanford has also put together a comment response tracking system, as have other sites, to coordinate the issues identified by stakeholders during the iterative planning and scoping phase and throughout the assessment process (which at this site will last for decades), and to track follow-ups.

A stakeholder involvement program is under way for an ongoing sitewide cumulative risk assessment and risk reduction project at the DOE Los Alamos National Laboratory (LANL) in New Mexico. This approach has been developed and is being implemented by the independent Risk Assessment Corporation (RAC) team is under the Risk Analysis, Communication, Evaluation, and Reduction (RACER) project. The primary objectives of this project are to develop:

1. A process for extensive stakeholder involvement in the risk assessment and decision-making processes for LANL.

2. A methodology to estimate contemporary (current) human health risks and ecological impacts from LANL using available data on chemicals and radionuclides measured in environmental media.

3. A methodology to implement a comprehensive risk-informed decision analysis framework, including a prospective risk and ecological impact assessment and other quantitative and qualitative criteria, to guide long-term management of risks and ecological impacts at LANL.

4. A consistent approach for efficiently compiling, using, and updating data to support the risk assessment and decision-making processes.

Guidelines developed by RAC for involving stakeholders in this project are included on the project website at http://www.racteam.com/LANLRisk/Reports/Guidelines%20for%20Involvement%2010-30.pdf. The RACER project is also involving local schools in science projects, including to provide input to exposure scenarios. This input is also being solicited in one-on-one meetings with others at various locations in the community (businesses and homes).

A much earlier scientific educational partnership was established more than a decade ago at the Weldon Spring site. Information about that Partners in Education program can be found at http://web.em.doe.gov/wssrap/pie.html. Every community will have its own priorities and levels of interest. More examples are given in Table A-1.

- **Data Quality Objectives and Assessment (U.S. EPA).** The Agency has developed a series of documents that provide guidelines to help ensure that the data collected are appropriate for their intended use (see Table A-1). These documents outline a systematic planning process for developing performance criteria for the collection, evaluation, and use of environmental data. This process can be used to focus communication among interested parties and to form the basis for selecting decision points for a risk assessment project. The overall approach is called the DQO process, and it is detailed in *Guidance for the Data Quality Objectives Process* (U.S. EPA, 2000g). The seven-step planning approach to develop sampling designs for data collection is iterative and applies to all scientific studies, but it is particularly useful for addressing problems that have two clear alternatives. The final outcome of the DQO process is a design for collecting data (including the number of samples, location of samples, and collection method) that acknowledges the limits on the data collection and the probabilities of making decision errors. Guidance can be found at http://www.epa.gov/quality/qs-docs/g4-final.pdf.

  The Agency has also developed Data Quality Assessment (DQA) guidance (U.S. EPA, 2000h) that describes procedures to help ensure that data used in risk assessments are appropriate for their intended use with respect to quality, quantity, and type. Also provided are statistical and analytical tools that can be used to review DQOs and sampling designs, review preliminary data, select statistical tests to summarize and analyze data, verify the assumptions of the statistical test, and perform appropriate calculations.

TABLE A-1

Selected Resources for Planning, Scoping, and Problem Formulation

Resource and Access	Purpose and Scope	Cumulative Risk Remarks
Resources for Overall Planning, Scoping, and Problem Formulation		
Framework for Cumulative Risk Assessment (U.S. EPA) http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=54944	Provides a flexible framework for cumulative risk assessments; identifies the basic elements of the process, describes a number of technical and coordination issues, and defines terms.	Defines general structure and components of cumulative risk assessments; serves as the foundation for this report.
Guidance on Cumulative Risk Assessment – Part 1, Planning and Scoping (U.S. EPA) http://www.epa.gov/OSA/spc/2cumrisk.htm	This guidance directs each office of U.S. EPA to take into account cumulative risk issues in scoping and planning major risk assessments and to consider a broader scope that integrates multiple sources, effects, pathways, stressors and populations for cumulative risk analyses in all cases for which relevant data are available. It describes general approaches and concepts for planning and scoping for cumulative risk assessments.	Identifies four key steps for planning and scoping: determine overall purpose and risk management objectives for assessment; determine the scope, problem statement, participants, and resources; determine the risk dimensions and technical elements that may be evaluated; and formulate a technical approach including a conceptual model and an analysis plan for conducting the assessment.
Lessons Learned on the Planning and Scoping of Environmental Risk Assessments (U.S. EPA) http://www.epa.gov/osa/spc/pdfs/handbook.pdf	Provides early feedback to agency scientists and managers regarding U.S. EPA's experiences with planning and scoping as the first step in conducting environmental assessments. It is intended to reinforce the importance of formal planning and dialogue prior to conducting complex cumulative assessments and to provide case studies "lessons learned" for anyone involved in planning an assessment.	Provides information and feedback from the Part 1 planning guidance that offer insights for designing and conducting cumulative risk assessments.

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TABLE A-1 cont.		
Resource and Access	Purpose and Scope	Cumulative Risk Remarks
Environmental Justice Geographic Assessment Tool (U.S. EPA) http://www.epa.gov/enviro/ej/	GIS-based module designed for front-end scoping of cumulative assessments. Combines environmental, socioeconomic, and health indicators in statistical tables. Initially developed to evaluate potential environmental justice (EJ) issues.	Allows interactive mapping and review of regulated facilities, environmental monitoring sites, bodies of water, land use, community demographics, streets/schools/hospitals. Can be adapted or linked as a module to assess cumulative risks for various communities (i.e., not limited to EJ issues).
SCEM Builder Model (DOE) http://tis.eh.doe.gov/oepa/programs/scem.cfm	Graphics tool designed to develop a site conceptual exposure model for a contaminated site.	General graphics tool that can be used to set up a conceptual model for the site, to guide stakeholder inputs for a cumulative risk assessment.
Risk Screening Environmental Indicators (RSEI) (U.S. EPA) http://www.epa.gov/opptintr/rsei/	Screening tool that compares toxic chemicals released to the environment from industrial sources. Offers way to examine rankings and trends and set priorities for further action.	Allows data to be sorted by chemical, media, and geographic area. Preliminary analyses can identify situations of relatively higher concern during scoping.
Resources for Stakeholder Involvement		
Community Air Screening How To Manual (U.S. EPA) http://www.epa.gov/oppt/cahp/howto.html	Explains how to form a partnership, clarify goals, develop a detailed local source inventory, use a risk-based process to identify priorities, and develop options for risk reduction. Developed by U.S. EPA's Office of Pollution Prevention and Toxics based on the Baltimore, MD, approach. (Expected to be published in spring 2004.)	Presents and explains a step-by-step process a community can follow to: form a partnership to access technical expertise, identify and inventory local sources of air pollutants, review these sources to identify known hazards that might pose a health risk to the community, and set priorities and develop a plan for making improvements. Covers only the air pathway.

TABLE A-1 cont.		
Resource and Access	Purpose and Scope	Cumulative Risk Remarks
Superfund Community Involvement Handbook, Appendix on Community Involvement Requirements (U.S. EPA) http://www.epa.gov/superfund/action/community/index.htm	Superfund guidance on suggested community involvement structure, communications, and approach. For contaminated Superfund sites, the lead agency informs public of the availability of technical assistance grants (TAG). TAG is a grant program that provides funds for citizen groups to hire independent technical advisors to help them understand/comment on technical decisions re: Superfund cleanup actions.	Developed for U.S. EPA's Superfund program, the information about community involvement, including forming community advisory groups (CAGs), is useful for cumulative risk assessments at contaminated sites.
Hanford Site, Hanford Advisory Board (HAB), Public Involvement Resources and Calendar (DOE site) http://www.hanford.gov/orp/?page=5&parent=1 http://www.hanford.gov/public/calendar/	The HAB was set up to provide recommendations and advice to DOE, U.S. EPA, and the Washington Department of Ecology on a number of issues related to cleanup of the Hanford site.	The HAB has developed mission language, a meeting schedule/calendar, and other information that can serve as examples for other projects.
Los Alamos National Laboratory (LANL) Risk Analysis, Communication, Evaluation, and Reduction (RACER) project (DOE site) http://www.racteam.com/LANLRisk/Reports/Guidelines%20for%20Involvement%2010-30.pdf	The RACER project is founded on extensive stakeholder involvement. Established by the RAC team, this project is developing an open process for assessing cumulative risks at LANL and for creating a decision analysis framework for risk reduction, as well as an integrated database (containing data from multiple collecting organizations) to support data evaluations and trend analyses, site risk assessments, and the overall decision-making process for environmental management at LANL. Stakeholder participation is actively sought, both open progress meetings and one-on-one meetings are held (in various settings), and the internet (project website and e-mail) is also used to announce upcoming activities and the availability of draft documents for stakeholder comment, and to solicit inputs.	Insights for cumulative assessments can be found in: RAC guidelines for stakeholder involvement, open survey questions, plans for soliciting (in various venues) and summarizing inputs to guide the assessment, and suggestions for pursuing grants for ongoing stakeholder involvement (aimed to be administered through an independent group), as well as other plans and products that can be found on the project website.

TABLE A-1 cont.		
Resource and Access	Purpose and Scope	Cumulative Risk Remarks
Community Air Screening How To Manual (U.S. EPA) http://www.epa.gov/oppt/cahp/howto.html	Explains how to form a partnership, clarify goals, develop a detailed local source inventory, use a risk-based process to identify priorities, and develop options for risk reduction. Developed by U.S. EPA's Office of Pollution Prevention and Toxics based on the Baltimore, MD, approach. (Expected to be published in spring 2004.)	Presents and explains a step-by-step process a community can follow to: form a partnership to access technical expertise, identify and inventory local sources of air pollutants, review these sources to identify known hazards that might pose a health risk to the community, and set priorities and develop a plan for making improvements. Covers only the air pathway.
Superfund Community Involvement Handbook, Appendix on Community Involvement Requirements (U.S. EPA) http://www.epa.gov/superfund/action/community/index.htm	Superfund guidance on suggested community involvement structure, communications, and approach. For contaminated Superfund sites, the lead agency informs public of the availability of technical assistance grants (TAG). TAG is a grant program that provides funds for citizen groups to hire independent technical advisors to help them understand/comment on technical decisions re: Superfund cleanup actions.	Developed for U.S. EPA's Superfund program, the information about community involvement, including forming community advisory groups (CAGs), is useful for cumulative risk assessments at contaminated sites.
Hanford Site, Hanford Advisory Board (HAB), Public Involvement Resources and Calendar (DOE site) http://www.hanford.gov/orp/?page=5&parent=1 http://www.hanford.gov/public/calendar/	The HAB was set up to provide recommendations and advice to DOE, U.S. EPA, and the Washington Department of Ecology on a number of issues related to cleanup of the Hanford site.	The HAB has developed mission language, a meeting schedule/calendar, and other information that can serve as examples for other projects.

TABLE A-1 cont.		
Resource and Access	Purpose and Scope	Cumulative Risk Remarks
Los Alamos National Laboratory (LANL) Risk Analysis, Communication, Evaluation, and Reduction (RACER) project (DOE site) http://www.racteam.com/LANLRisk/Reports/Guidelines%20for%20Involvement%2010-30.pdf	The RACER project is founded on extensive stakeholder involvement. Established by the RAC team, this project is developing an open process for assessing cumulative risks at LANL and for creating a decision analysis framework for risk reduction, as well as an integrated database (containing data from multiple collecting organizations) to support data evaluations and trend analyses, site risk assessments, and the overall decision-making process for environmental management at LANL. Stakeholder participation is actively sought, both open progress meetings and one-on-one meetings are held (in various settings), and the internet (project website and e-mail) is also used to announce upcoming activities and the availability of draft documents for stakeholder comment, and to solicit inputs.	Insights for cumulative assessments can be found in: RAC guidelines for stakeholder involvement, open survey questions, plans for soliciting (in various venues) and summarizing inputs to guide the assessment, and suggestions for pursuing grants for ongoing stakeholder involvement (aimed to be administered through an independent group), as well as other plans and products that can be found on the project website.
Savannah River Site Citizen's Advisory Board (CAB) (DOE site) http://www.srs.gov/general/outreach/srs-cab	The CAB provides advice and recommendations DOE, U.S. EPA, and the South Carolina Department of Health and Environmental Control on environmental remediation, waste management and related issues. Meetings and public comment sessions are held regularly and are open to the public.	Recommendations and information on workshops published on this website can offer insights for similar projects.
Multnomah County Protocol for Assessing Community Excellence in Environmental Health (PACE-EH) http://www.pace-eh.org	Pilot assessments performed in five neighborhoods of Portland, Oregon, resulted from a community health assessment team's efforts to prioritize environmental health concerns.	Multipathway issues identified that can offer insights for other studies include poor indoor air quality (including mold and mildew), exposure to lead-based paint, and unsafe grounds.

TABLE A-1 cont.		
Resource and Access	Purpose and Scope	Cumulative Risk Remarks
Onondaga Lake Partnership (OLP) website http://www.onlakepartners.org	Aim is to promote cooperation among government agencies and others involved in managing environmental issues of Onondaga Lake and the Onondaga Lake watershed in Syracuse, New York. The website presents information about pollutants, health risks, cleanup projects, and opportunities for public involvement in this complex cleanup project for a heavily polluted lake in a major metropolitan area, with high level of public concern.	Similar to previous example, illustrates how a variety of scientific information, documents, program management information, presentations, video clips, image gallery, and an e-mail announcement list can be shared for cumulative risk assessment projects.
Depleted Uranium Hexafluoride Management Information Network (DOE project) http://www.ead.anl.gov/uranium	Presents information for the DOE inventory of depleted uranium hexafluoride (DUF6). Includes basic scientific information on uranium, depleted uranium, and DUF6; the DOE program for managing the DUF6 inventory; research and development for beneficial uses of DU, and public involvement opportunities. Environmental impact statements (EISs) and other reports are included. (Several hundred thousand visitors since 1997.) Used comment response management system (CRMS), web-enabled software which expedites responses to government and public comments about this and other EISs.	Similar to previous example, illustrates how various reports, presentations, video clips, image gallery, and an e-mail announcement list can be shared for a cumulative risk assessment project.
Resources for Guiding Data Quality		
Guidance for the Data Quality Objectives Process (QA/G-4) (U.S. EPA) http://www.epa.gov/quality/qs-docs/g4-final.pdf	Guidance on the data quality objectives (DQO) process, a systematic planning process for environmental data collection. Designed to help risk assessors ensure that data are collected for a specific purpose. Includes determination of chemicals to evaluate or test for, media and locations of concern, and detection limits.	Developed for the recommended planning process when environmental data are used to select between two opposing conditions, this general guidance is useful for cumulative assessments. Focus is placed on the cumulative risk questions to be answered, while maintaining awareness of appropriate statistical techniques that should be considered to produce defensible results.

TABLE A-1 cont.		
Resource and Access	Purpose and Scope	Cumulative Risk Remarks
Decision Error Feasibility Trials (DEFT) Software (QA/G-4D) (U.S. EPA) http://www.epa.gov/quality/qs-docs/g4d-final.pdf	Computer-based software for determining the feasibility of data quality objectives defined using the DQO process. Enables statistical sample size planning and can be used to estimate costs associated with obtaining a specific precision in environmental data (such as how many samples are required to determine whether environmental concentrations are above or below background or risk-based concentrations).	General analytical guidance can be applied to multiple media and multiple contaminants. This tool calculates the appropriate number of environmental samples required to statistically answer whether soil or water concentrations are above or below a risk-based level, which could be adapted to grouped chemicals.
Guidance on Choosing a Sampling Design for Environmental Data Collection (QA/G-5S) (U.S. EPA) http://www.epa.gov/quality/qs-docs/g5s-final.pdf	Guidance on applying standard statistical sampling designs (such as simple random sampling) and more advanced sampling designs (such as ranked set sampling, adaptive cluster sampling) to environmental applications.	Can be useful to identify co-located contaminants to support grouping for a cumulative risk assessment at a contaminated site or situation.
Guidance for Quality Assurance Project Plans for Modeling (QA/G-5M) (U.S. EPA) http://www.epa.gov/quality/qs-docs/g5m-final.pdf	General guidance for developing quality assurance project plans (QAPPs) for modeling projects.	Can be useful to cumulative risk assessments, particularly where air or groundwater models are needed to extrapolate small data sets to the site or community level.
Guidance on Environmental Data Verification and Data Validation (QA/G-8) (U.S. EPA) http://www.epa.gov/quality/qs-docs/g8-final.pdf	Guidance to help organizations verify and validate data. Applying this to laboratory analytical data allows risk assessors to understand uncertainties associated with concentration measurements (which impact assessment results).	Useful for determining appropriate data for the chemicals to be evaluated in a cumulative risk assessment; important to results, especially when using conservative screening approaches.

TABLE A-1 cont.		
Resource and Access	Purpose and Scope	Cumulative Risk Remarks
Guidance for Data Quality Assessment: (DQA): Practical Methods for Data Analysis (QA/G-9) (U.S. EPA) http://www.epa.gov/quality/qs-docs/g9-final.pdf	Describes procedures and methodologies for ensuring sound data are used in the risk assessment. Provides tools that can be used to review DQOs and sampling design, review preliminary data, select statistical tests to summarize and analyze data, verify the assumptions of the statistical test, and perform calculations.	These tools can indicate differences in the statistical robustness that might affect data combinations for chemical groupings/selection of representative concentrations. For instance, if certain data were collected according to DQOs established with DEFT (see earlier entry) while other data were collected under a different program that required fewer samples, then care must be taken when combining those data.

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A.2. RESOURCES FOR ENVIRONMENTAL FATE AND TRANSPORT ANALYSES

Several tools that can be used to evaluate environmental fate and transport of chemicals to support cumulative health risk assessments are highlighted below. Selected information is summarized in Table A-2 at the end of this section.

- **ChemFinder Database (Private, via U.S. EPA).** The ChemFinder database is an online, U.S. EPA-linked search engine that provides access to information on the chemical, physical, product, and biological properties of a large number of chemicals. Developed by Cambridgesoft, this tool can be searched by common name, brand name, Chemical Abstract Service (CAS) number, chemical formula, or other designations, including chemical structure. ChemFinder searches chemical information from a large pool of websites worldwide, including government and multilateral agencies, universities, and private institutions. The ChemFinder search engine is available for free use via the U.S. EPA Office of Pesticide Programs at http://www.epa.gov/oppfead1/pmreg/pits/index.html and can also be found at http://chemfinder.cambridgesoft.com/.

- **Risk Assessment Protocols for Hazardous Waste Combustion Facilities (U.S. EPA).** In 1998, U.S. EPA Region 6 identified the need for a guidance document that consolidated information presented in earlier Agency documents and in reports from state environmental agencies, to provide an integrated set of procedures for conducting site-specific combustion risk assessments addressing multiple sources and exposure scenarios. Two documents were prepared: the *Human Health Risk Assessment Protocol for Hazardous Waste Combustion Facilities* (HHRAP; U.S. EPA, 2005d), and the *Screening Level Ecological Risk Assessment Protocol for Hazardous Waste Combustion Facilities* (SLERAP; U.S. EPA, 1999f). The objectives of these documents were to (1) apply the best available methods for evaluating risk to human health and the environment from operations of hazardous waste combustion units, and (2) develop repeatable and documented methods for consistency and equity in permitting decisions.

  In addition to providing methodologies for evaluating multi-media, multi-pathway risks, Volume II of the guidance contains information and data on the chemical, physical, and environmental properties of many chemicals that can be used to model environmental fate and transport and exposure. These data can also be used to predict what chemicals are likely to behave similarly in the environment, to support groupings for cumulative risk assessments.

- **Soil Screening Guidance (U.S. EPA).** The Agency has developed an extensive set of environmental and physical constants and parameters that can be used to model the fate and transport of chemicals in soil and to develop risk-based soil screening levels (SSLs) to protect human health (U.S. EPA, 1996a).

The primary goal is to provide simple screening information and a method for developing site-specific screening levels, so it also serves as a tool to support exposure-based screening. The guidance includes both detailed models and generic SSLs, which can be used to quickly (and conservatively) assess what areas or pathways might not warrant a detailed assessment. Developed for use at National Priorities List sites, the concepts can be extended to other sites and situations. The guidance also includes tables of chemical-specific constants, such as the organic carbon partition coefficient (Koc), the soil-water partition coefficient (Kd), and water and air diffusivity constants (Di,w and Di,a), to support the evaluation of fate and transport.

- **Background Determinations (U.S. EPA, Others).** Concentrations that appropriately represent "background" levels (naturally occurring or ambient) are location-specific and help provide context for the fate and transport of site chemicals. The Agency has prepared extensive guidance on various approaches for characterizing background, as well as protocols for determining whether a contaminated site's concentrations are statistically above background. For example, see *Guidance for Characterizing Background Chemicals in Soil at Superfund Sites* (U.S. EPA, 2001e).

  Data on background concentrations of inorganics (notably in soil) can be found in several sources, and these data can provide an initial general context for site- or community-specific risk analyses. The information sources include toxicological profiles developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and reports from the U.S. Geological Survey and universities. Agency sources include the *Ecological Soil Screening Level Guidance* (U.S. EPA, 2004e), which gives 50 state-specific ranges, and regional guidelines, and "typical" values provided as technical background to risk-based screening levels (U.S. EPA, 2002g, 2003i). The U.S. EPA Region 6 includes background concentrations in its *Human Health Medium-Specific Screening Levels* document (U.S. EPA, 2005e), and the associated database contains screening values and the physical and chemical parameters that were used to derive those values.

  Background data can also be found in state-specific documents, such as the Texas Risk Reduction Program Guidelines (TCEQ, 1999), which include background concentrations for the state. The Massachusetts Department of Environmental Protection (MADEP) has published state-specific background levels of PAHs and metals in soil (http://www.tceq.state.tx.us/assets/public/remediation/trrp/350revisions.doc) (MADEP, 2002). City or other location-specific resources can also be found (as described in Chapter 3 of this report), such as the City of Chicago Department of Environment values for "background" PAHs (CCDE, 2003), which have been adopted by Illinois EPA as indicative of PAH concentrations in Chicago soil (see http://www.epa.state.il.us/land/site-remediation/urban-area-pah-study.pdf).

- **Vapor Intrusion (U.S. EPA, Others).** Vapor intrusion can be an important pathway when volatile organic chemicals in subsurface media (soil, groundwater, and non-aqueous phase liquids) could migrate to air inside a building. Risks from this pathway are often combined with other exposure pathways for indoor air (e.g., inhalation of volatiles during showering) to quantify aggregate risks for single chemicals (e.g., benzene) and cumulative risks for a group of chemicals (e.g., chlorinated solvents).

  This pathway has been evaluated using a model based on the allometric equation given in Johnson and Ettinger (1991). That model is a one-dimensional spreadsheet that estimates convective and diffusive transport of chemical vapors to indoor air from sources near a building's perimeter. The model ignores attenuating factors (e.g., biological degradation) and assumes an infinite source over the exposure duration of the receptor (e.g., 25 years for a commercial or industrial worker). A detailed description of the vapor intrusion model is provided in draft *Guidance for Evaluating the Vapor Intrusion to Indoor Air Pathway from Groundwater and Soils* (U.S. EPA, 2002h) and the draft *User's Guide for Evaluating Subsurface Vapor Intrusion into Buildings* (U.S. EPA, 2003j). Separate versions of the spreadsheet model are available for evaluating potential source concentrations (e.g., soil gas or groundwater data).

  Both screening-level and advanced versions of the models are available for each. The screening-level version limits user inputs to the most sensitive parameters and allows the user to define only a single soil stratum above the source. The advanced version allows users to enter additional site-specific data for soil and building parameters and incorporates up to three soil strata for which soil properties can be varied. In February 2003, the U.S. EPA released Version 3.0 of the vapor intrusion model, which contained updated toxicity values and other physical/chemical parameters. This model and associated guide are still undergoing review. Certain state agencies (e.g., California) have modified that model to include state-sanctioned toxicity values or other model parameters (DTSC, 2003). Other organizations are also developing approaches (including other federal agencies).

  While the Johnson and Ettinger model is most widely recognized for vapor intrusion, several states have adopted simple equations based on this methodology to evaluate the indoor air pathway on a screening level. For example, the Risk Evaluation/Corrective Action Program (RECAP) of the Louisiana Department of Environmental Quality (LDEQ) has developed a set of publicly available spreadsheets that contain equations and chemical-specific information that can be used to predict conservative concentrations of VOCs in indoor air for industrial and nonindustrial buildings constructed over groundwater plumes. Chemical concentration values for multiple chemicals calculated by the models could be combined to evaluate cumulative exposure.

- **Fate and Transport/Risk Assessments (U.S. EPA, Others).** For risk assessments at contaminated sites, urban environments and other situations potentially impacted by multiple sources or sources distant from the population of concern, it is often necessary to simulate the behavior of multiple chemicals in different environmental media. Hundreds of computer models have been developed to model various aspects of horizontal and vertical contaminant fate and transport in the environment. Some are very general and conceptual, while others are quite specific to certain media characteristics and applications. The use and applicability of individual models varies widely depending on the project objectives and specificity required, so it is important for the model chosen to be appropriate for the given site setting. For example, the Center for Subsurface Modeling Support (CSMoS) within U.S. EPA's Office of Research and Development (ORD) (located in Ada, Oklahoma) maintains an online database of public groundwater and vadose zone fate and transport models. This database is accessible at http://www.epa.gov/ada/csmos.html.

  Other tools that support characterization and modeling of the movement and behavior of chemicals in the environment include the U.S. EPA Soil Screening Guidance (described above), as well as environmental data compiled by many organizations for specific regions and conditions. Data of interest typically include soil type (e.g., sand, loam, clay); drainage characteristics, hydraulic conductivity, depth to groundwater, water quality parameters, organic carbon content, and various other constants and coefficients.

  Environmental data are also available through databases maintained by the U.S. Geological Survey (USGS), state natural resources departments, colleges and universities, U.S. Department of Agriculture (USDA) Natural Resources Conservation Service (NRCS) field offices (offices in most county seats), USDA soil surveys (available for most counties at NRCS offices and local libraries), scientific textbooks and journals, internet resources, and professional organizations. Other organizations have also developed groundwater models that can be used for cumulative risk assessments (not available through the U.S. EPA website), as indicated in Table A-2.

TABLE A-2

Selected Resources for Evaluating Fate and Transport

Resource and Access	Purpose and Scope	Cumulative Risk Remarks
Soil Screening Guidance (U.S. EPA) http://www.epa.gov/superfund/resources/soil/introtbd.htm	Provides tools for developing screening levels for, and conducting, risk assessments involving soil and groundwater. Useful input parameters and technical background for environmental models.	Standard constants, coefficients, and soil data that can be useful to cumulative risk assessments.
SESOIL (SEasonal SOIL compartment model) In the public domain, although updated versions are available from RockWare, Inc. http://www.rockware.com/	SESOIL is a one-dimensional vertical transport screening-level model for the unsaturated (vadose) zone that can be used to simulate the fate of contaminants in soil to support site-specific cleanup objectives. Simulates natural attenuation based on diffusion, adsorption, volatilization, biodegradation, cation exchange, and hydrolysis. The model can evaluate one chemical at a time; does not predict interactions in environmental media.	Results can indicate how far a contaminant plume will migrate; predicted concentrations can be compared to media-specific standards and can be used to estimate single-chemical risks based on standard default exposure parameters, locations, and times. The location- and time-specific predictions for single chemicals can be overlain to support grouping decisions for a cumulative assessment.
AT123D (Analytical Transient 1-, 2-, and 3-Dimensional simulation of waste transport in the aquifer system) http://www.scisoftware.com/	Generalized three-dimensional groundwater transport and fate model. Transport and fate processes simulated include advection, dispersion, adsorption and biological decay. The model can evaluate one chemical at a time; does not predict interactions in environmental media.	As above.
Summers model http://www.seview.com/	Screening level leachate program that estimates groundwater concentrations based on mixing. Simulates dilution of soil in groundwater. The model can evaluate one chemical at a time; does not predict interactions in environmental media.	As above.

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TABLE A-2 cont.		
Resource and Access	Purpose and Scope	Cumulative Risk Remarks
Draft guidance and user's guide for evaluating vapor intrusion into buildings (U.S. EPA); LDEQ spreadsheets to screen vapor intrusion pathway	Provides a model to estimate convective and diffusive transport of chemical vapors to indoor air. Could offer insights where indoor air exposures are a concern. (Currently under review.) LDEQ provides set of equations that enable screening of the vapor intrusion pathway.	Model output can be used to support cumulative risk assessments, as concentrations of multiple chemicals can be evaluated simultaneously.
(The following models are available for download from the CSMoS website, http://www.epa.gov/ada/csmos/models.html.)		
2DFATMIC and 3DFATMIC	Simulates subsurface flow, transport, and fate of contaminants that are undergoing chemical and/or biological transformations. Applicable to transient conditions in both saturated and unsaturated zones. The model can evaluate one chemical at a time; does not predict interactions in environmental media.	Results can indicate how far a contaminant plume will migrate; predicted concentrations can be compared to media-specific standards and can be used to estimate single-chemical risks based on standard default exposure parameters, locations, and times. The location- and time-specific predictions for single chemicals can be overlain to support grouping decisions for a cumulative assessment.
BIOCHLOR	Screening model that simulates remediation by natural attenuation of dissolved solvents at sites with chlorinated solvents. Can be used to simulate solute transport without decay and solute transport with biodegradation modeled as a sequential first-order process within one or two different reaction zones. The model can evaluate one chemical at a time; does not predict interactions in environmental media.	As above

TABLE A-2 cont.		
Resource and Access	Purpose and Scope	Cumulative Risk Remarks
BIOPLUME II and BIOPLUME III	Two-dimensional contaminant transport under the influence of oxygen-limited biodegradation (BIOPLUME II) and under the influence of oxygen, nitrate, iron, sulfate, and methanogenic biodegradation (BIOPLUME III). Models advection, dispersion, sorption, biodegradation (aerobic and anaerobic) and reaeration (BIOPLUME II) and through instantaneous, first order, zero order, or Monod kinetics (BIOPLUME III). BIOPLUME III was developed primarily for the modeling of natural attenuation of organic contaminants in groundwater; it is particularly useful at petroleum-contaminated sites. The model can evaluate one chemical at a time; does not predict interactions in environmental media.	As above
BIOSCREEN	Screening-level groundwater transport model that simulates natural attenuation of dissolved-phase hydrocarbons. Based on the Domenico analytical contaminant transport model and can simulate natural attenuation based on advection, dispersion, adsorption and biological decay. Estimates plume migration to evaluate risk at specific locations and times. The model can evaluate one chemical at a time; does not predict interactions in environmental media.	As above

TABLE A-2 cont.

Resource and Access	Purpose and Scope	Cumulative Risk Remarks
(The following models are available for download from the CSMoS website, http://www.epa.gov/ada/csmos/models.html, except as indicated.)		
CHEMFLO	Simulates one-dimensional water and chemical movement in the vadose zone. Models advection, dispersion, first-order decay and linear sorption. The model can evaluate one chemical at a time; it does not predict interactions in environmental media.	Results can indicate how far a contaminant plume will migrate; predicted concentrations can be compared to media-specific standards and can be used to estimate single-chemical risks based on standard default exposure parameters, locations, and times. The location- and time-specific predictions for single chemicals can be overlain to support grouping decisions for a cumulative assessment.
GEOEAS	Enables geostatistical analysis of spatially correlated data. Can perform basic statistics, scatter plots/linear and nonlinear estimation (kriging). The model can evaluate one chemical at a time; it does not predict interactions in environmental media.	As above.
GEOPACK	Enables geostatistical analysis of spatially correlated data. Can perform basic statistics, variography, linear and nonlinear estimation (kriging). The model can evaluate one chemical at a time; it does not predict interactions in environmental media.	As above.

TABLE A-2 cont.		
Resource and Access	Purpose and Scope	Cumulative Risk Remarks
HSSM	Can simulate: light non-aqueous phase liquid (LNAPL) flow and transport of a chemical constituent of the LNAPL from the ground surface to the water table; radial spreading of the LNAPL phase at the water table; and dissolution and aquifer transport of the chemical. One-dimensional in the vadose zone, radial in the capillary fringe, two-dimensional vertically averaged analytical solution of the advection-dispersion equation in the saturated zone. The model can evaluate one chemical at a time; it does not predict interactions in environmental media.	As above.
Visual MODFLOW (available for a fee from the developer) and MODFLOW (U.S. Geological Survey), many iterations/updates; most recent is MODFLOW-2000	One of the most accessible and widely used models available. Numerically solves the three-dimensional ground-water flow equation for a porous medium by using a finite-difference method. Visual MODFLOW output is graphic, including two- and three-dimensional maps; designed to model flow, can evaluate one chemical at a time (information input by user); it does not predict interactions in environmental media.	As above.

TABLE A-2 cont.

Resource and Access	Purpose and Scope	Cumulative Risk Remarks
(The first three models below are available for download from the CSMoS website, http://www.epa.gov/ada/csmos/models.html.)		
PESTAN	Vadose zone modeling of the transport of organic pesticides. Models advection, dispersion, first-order decay and linear sorption. The model can evaluate one chemical at a time; it does not predict interactions in environmental media.	Results can indicate how far a contaminant plume will migrate; predicted concentrations can be compared to media-specific standards and can be used to estimate single-chemical risks based on standard default exposure parameters, locations, and times. The location- and time-specific predictions for single chemicals can be overlain to support grouping decisions for a cumulative assessment.
Soil Transport and Fate (STF) Database	Database providing information concerning the behavior of organic and a few inorganic chemicals in the soil environment. Focus is on one chemical at a time; interactions not addressed.	General-use tool can be used to evaluate environmental contaminants for cumulative risk assessments.
UTCHEM	Three-dimensional model that simulates non-aqueous phase liquid (NAPL) movement in the subsurface. Can address: multiple phases; dissolution and/or mobilization by non-dilute remedial fluids; chemical and microbiological transformations; and changes in fluid properties as a site is remediated.	General-use tool can be used to evaluate environmental contaminants for cumulative risk assessments. Interesting for cumulative risk because NAPL is commonly a complex mixture itself and can be present in multiple phases, which are assessed by the model.
MT3D (links to MODFLOW) http://www.ess.co.at/ECOSIM/MANUAL/mt3d.html	Three-dimensional transport model for simulating advection, dispersion, and chemical reactions in groundwater systems; assumes first-order decay. Can address one chemical at a time.	Chemical reaction can be addressed with a loss term (information on chemical must be input by user) but degradation product not tracked. Heavily dependent on extensive characterization of site setting (can be hard to get sufficient data for all parameters needed).

TABLE A-2 cont.		
Resource and Access	Purpose and Scope	Cumulative Risk Remarks
SWIFTIII (private)	Three-dimensional flow (transient and steady state) and solute transport (advection, dispersion, sorption and decay) in fractured porous media; uses finite difference method; addresses chemical reactions with second-order decay; also models radionuclides.	Similar to above, but can address more than one chemical: parent plus degradation product(s) (chain of two). (As above, user must input information about each chemical.)
MULKOM codes, including TMVOC (and predecessor T2VOC) (DOE/Lawrence Berkeley Laboratory, http://www-esd.lbl.gov/TOUGH2	Three-dimensional, three-phase flow of water, air, and volatile organic compounds in saturated and unsaturated zone to support remediation (e.g., soil vapor extraction). TMVOC can address more than one volatile organic (e.g., to model a spill of fuel hydrocarbons or solvents).	Similar to above, but can address a mixture of volatile organic compounds. Like the others models, depends heavily on extensive site setting characterization (hard to get data needed for all parameters, for results to be meaningful).

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A.3. RESOURCES FOR EXPOSURE ANALYSES

Many exposure models are well suited to assessing multiple exposures to multiple chemicals at contaminated sites and other multimedia situations, although this is generally performed by combining predictions for individual chemicals. Tools range from relatively straightforward screening models to comprehensive multimedia, multiple-pathway exposure models, as summarized below and in Table A-3 at the end of this section. Certain models presented here also support other portions of the risk assessment process. For example, the model for subsurface vapor migration soil (Johnson and Ettinger, 1991) is commonly considered an environmental fate and transport tool, but it can also serve as a multimedia exposure assessment resource because it considers both soil and groundwater inputs to predict concentrations in indoor air. Several supporting documents are also available that provide exposure factors, their bases, and receptor parameters that are used in various exposure models.

- **Exposure Factors (U.S. EPA).** Risk assessments rely on exposure models to represent various environmental and receptor-specific factors that can affect exposures to chemicals. For example, exposure factors cover exposure duration, time involved in certain activities, body weight and surface area, intake rates (e.g., inhalation, ingestion of food, soil, water), and many others parameters needed to estimate representative risks. The Agency has summarized extensive data in a set of exposure factor handbooks based on many studies, which consider statistical and relative contributions of many potential sources of human exposures to chemicals in air, drinking water, vapor, food, and soil. These handbooks include:

  - *Exposure Factors Handbook, Volume I – General Factors* (U.S. EPA, 1997c), see www.epa.gov/ncea/pdfs/efh/front.pdf.

  - *Exposure Factors Handbook, Volume II – Food Ingestion Factors* (U.S. EPA, 1997c), see www.epa.gov/ncea/pdfs/efh/front.pdf.

  - *Exposure Factors Handbook, Volume III – Activity Factors* (U.S. EPA, 1997c), see www.epa.gov/ncea/pdfs/efh/front.pdf.

- *Child-Specific Exposure Factors Handbook (Interim Report)* (U.S. EPA, 2002i), see http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55145.

- *Sociodemographic Data Used for Identifying Potentially Highly Exposed Populations* (U.S. EPA, 1999c), see http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=428679.

- Fact Finder CD-ROM searches data from the *Exposure Factors Handbook* and *Sociodemographic Data Used for Identifying Potentially Highly Exposed Populations* (referenced above), see http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=23650.

- **3MRA Model (U.S. EPA).** The 3MRA model is a multimedia, multipathway, multireceptor exposure and risk assessment model being developed by the Agency to assess releases from land-based waste management units. After simulating releases from disposal units, modules model fate and transport through the environment, estimate exposure to receptors, and calculates distributions of risks to receptors. This screening-level model is intended to be applied on a site-specific basis to generate risk-based standards (considering exit levels, e.g., to exit from specific regulations). Risks are assessed at individual sites to provide input to a representation a national distribution of risks. The national distribution of risks is the basis for determining waste stream constituent concentrations that meet regulatory criteria established to be protective of human health and ecological receptors (as determined by U.S. EPA policy). To establish national regulatory limits, site-based risk results are combined to evaluate national risk (i.e., to determine the percentage of nationwide receptors that are protected at various levels). For example, from this information a limit might be established to ensure protection of 95% of all receptors within 2 miles of a waste management unit at all sites across the nation. The 3MRA methodology uses a Monte Carlo scheme to quantify uncertainty (e.g., from natural variability or based on selection of representative sites). The resulting national criteria would represent threshold waste concentrations not considered hazardous (and not requiring Subtitle C disposal). The model is available at http://www.epa.gov/ceampubl/mmedia/3mra/.

- **Exposure and Fate Assessment Screening (E-FAST) Tool (U.S. EPA).** This computer-based model can provide screening-level estimates of general population, consumer, and environmental exposures to concentrations of chemicals released to air, surface water, landfills, and from consumer products. Potential inhalation, dermal and ingestion doses resulting from these releases are estimated. Modeled concentrations and doses are designed to reasonably overestimate exposures for use in screening-level assessments. The model is available from http://www.epa.gov/opptintr/exposure/docs/efast.htm.

- **Lead Exposure (U.S. EPA).** The traditional reference dose approach used to estimate health risks does not apply to lead because most human health effects data are based on blood lead concentrations rather than external dose. Blood

lead concentration is an integrated measure of internal dose, reflecting total exposure from all sources (e.g., both site-related and background sources for Superfund sites) (ATSDR, 1999a). Both U.S. EPA and the California EPA Department of Toxic Substances Control (CalEPA DTSC) have developed models to estimate blood lead concentrations from exposures to lead from various media, including soil, water, air, and food. The U.S. EPA tool for evaluating lead risks (the All Ages Lead Model) (U.S. EPA, 2005h) predicts lead concentrations in body tissue and organs for a hypothetical individual based on a simulated lifetime of lead exposure, and then extrapolates to a population of similarly exposed individuals.

The Agency has also developed a set of models for evaluating lead exposures and risks for non-residential adults. The models and supporting literature, methodologies, and technical information for these analyses are available at http://www.epa.gov/superfund/programs/lead/products.htm. Documents on the website include descriptions of how bioavailability and uptake factors for the adult lead model were determined. Examples of useful support documents also available from U.S. EPA include Revised *Interim Soil Lead Guidance for CERCLA Sites and RCRA Corrective Action Facilities* (U.S. EPA, 1994) and *Frequently Asked Questions on the Adult Lead Model* (U.S. EPA, 1999g).

- **The National Human Exposure Assessment Survey (NHEXAS) (U.S. EPA**). NHEXAS was developed by U.S. EPA's Office of Research and Development (ORD) in the early 1990s to provide critical information about multipathway, multimedia population exposure distribution to chemical classes. The first phase consisted of three pilot studies with the objectives of: evaluating the feasibility of NHEXAS concepts, methods, and approaches for the conduct of future population-based exposure studies; evaluating the utility of NHEXAS data for improved risk assessment and management decisions; testing the hypothesis that the distributions of exposure given by modeling and extant data do not differ from the measurement-based distributions of exposure; defining the distribution of multipathway human exposures for a relatively large geographic area; and stimulating exposure research and forging strong working relationships between government and nongovernment scientists. The NHEXAS web site is located at http://www.epa.gov/nerl/research/nhexas/nhexas.htm. NHEXAS data are available in the Human Exposure Database System (HEDS) at http://www.epa.gov/heds/.

- **Hotspots Analysis and Reporting Program (HARP) Tool (California Air Resources Board, CARB).** The State of California's Air Toxics "Hot Spots" program requires stationary air emission sources within the state to report the types and quantities of certain substances routinely release into the air. The recent HARP software package is designed to create and manage facility emissions inventory databases; prioritize facilities; model atmospheric dispersion of chemicals from one or multiple facilities using U.S. EPA models ISCST3 and BPIP; calculate cancer and noncancer (acute and chronic) health impacts using

guidance developed by CalEPA (in 2003); use point estimates or data distributions of exposures to calculate inhalation and multipathway risks; perform stochastic health risk analyses; calculate potential health effects for individual receptors, population exposures, cumulative impacts for one or multiple facilities and one or multiple pollutants, and potential health effects using ground-level concentrations; and present results as tables and isopleth maps. The results can be printed, added to word processing documents, or input to a Geographic Information Systems (GIS) program. The HARP model can be downloaded from http://www.arb.ca.gov/toxics/harp/downloads.htm#2.

- **Dietary Exposure Potential Model (DEPM) (U.S. EPA).** The DEPM estimates dietary exposure to multiple chemicals based on data from several national, government-sponsored food intake surveys and chemical residue monitoring programs. The DEPM includes recipes developed specifically for exposure analyses that link consumption survey data for prepared foods to the chemical residue information, which is normally reported for raw food ingredients, to estimate daily dietary exposure. Consumption in the model is based on 11 food groups containing approximately 800 exposure core food types, established from over 6500 common food items. The summary databases are aggregated in a way that allows the analyst to select appropriate demographic factors, such age/sex groups, geographical regions, ethnic groups and economic status. The model also includes modules for evaluating chemical exposures from residues, soil, and tap water. The model is available from U.S. EPA's National Exposure Research Laboratory (NERL) at http://www.epa.gov/nerlcwww/depm.htm.

- **Health Registries (Centers for Disease Control and Prevention, CDC; Others).** Several organizations maintain databases that contain information on the frequencies and types of diseases and other health-related information, such as on cancer, asthma, and birth defects, and blood lead levels. This information can be evaluated in concert with modeled or measured chemical exposure data to correlate potential influences of multiple exposures and to calibrate risk models. For example, the CDC maintains a national registry of cancer cases, including cancer type and target tissue, as well as demographic and location information.

  Many states have established cancer and other disease registries to monitor trends over time; determine patterns in various populations; guide planning and evaluation of control programs; help set priorities for allocating health resources; advance clinical, epidemiologic, and health services research; and provide information for a national database of cancer incidence. The National Cancer Registry is searchable online http://www.cdc.gov/cancer/natlcancerdata.htm. The CDC website also contains links to various state registries. Other resources that can be useful for identifying populations at potential risk include the U.S. Census Bureau (http://www.census.gov/), state and local government health departments, and other health organizations. An additional useful resource is the

report *Sociodemographic Data Used for Identifying Potentially Highly Exposed Populations* (U.S. EPA, 1999c).

- **National Occupational Research Agenda (NORA) (National Institute for Occupational Safety and Health, NIOSH).** Within NIOSH, NORA has identified a number of research areas for mixed occupational exposures, with an aim to protect individuals in the workplace from exposures to multiple chemicals. The mixed exposures team website (http://www2a.cdc.gov/nora/noratopictemp.asp?rscharea=me) provides links to current and past studies, as well as information on how to join a listserv group to discuss topics related to mixed exposures. Scientific knowledge developed through this effort can offer insights for assessing combined the effects of chemicals at contaminated sites, occupational settings and other scenarios involving multiple chemicals.

- **Tool for the Reduction and Assessment of Chemical and Other Impacts (TRACI) (U.S. EPA).** TRACI is an impact assessment tool for assessing multiple chemical impact and resource-use categories to analyze various study designs. Impacts that can be modeled include: ozone depletion; global warming; acidification; eutrophication; photochemical smog; cancer risk and noncancer health effects; human health criteria; ecotoxicity; fossil fuel use; land use; and water use. The program includes quantitative data on human carcinogenicity and noncarcinogenicity (based on human toxicity potentials), acidification, smog formation, and eutrophication. The model uses a probabilistic approach to determine spatial scale(s) for other impact categories such as acidification, smog formation, eutrophication, and land use. Information is available at http://www.epa.gov/ordntrnt/ORD/NRMRL/pubs/600r02052/600r02052.htm .

- **Technology Transfer Network, TTN (U.S. EPA).** This is an on-line information resource for tools to support air pathway analyses. The TTN maintains a Clearinghouse for Inventories and Emission Factors (CHIEF) website (http://www.epa.gov/ttn/chief/) that contains links to many of the relevant documents on methods and data for constructing emissions inventories available for download, including the *Handbook for Criteria Pollutant Inventory Development: A Beginner's Guide for Point and Area Sources* (U.S. EPA, 1999h); *Handbook for Air Toxics Emission Inventory Development, Volume I: Stationary Sources* (U.S. EPA, 1998e); and *Compilation of Air Pollutant Emission Factors* (U.S. EPA, 1995c et seq.). U.S. EPA also maintains a Support Center for Regulatory Air Models (SCRAM) website (http://www.epa.gov/ttn/scram/), which provides information on codes described in the *Guideline on Air Quality Models* (U.S. EPA, 2003d), and includes downloadable models and guidance. Information from TTN is included in the discussion of the air pathway in Section 4.4 of this report.

TABLE A-3

Selected Resources for Evaluating Exposure

Resource and Access	Purpose and Scope	Cumulative Risk Remarks
Exposure Factors Guidance (U.S. EPA) general: http://www.epa.gov/ncea/pdfs/efh/front.pdf child: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55145	Provides extensive values and underlying bases for many factors that affect exposures. Examples include exposure duration, frequency, surface area, inhalation rates per activity level and age/gender, as well as ingestion rates, including for incidental soil ingestion and by food type, based on age and gender. Because children are often more heavily exposed to environmental toxicants than adults, U.S. EPA also published the *Child-Specific Exposure Factors Handbook* is to provide a summary of the available and up-to-date statistical data on various factors assessing children exposures.	Excellent compendium of values for exposure parameters that can be reviewed to determine those most appropriate for a given site/setting (for both adults and children). Can be used to assess multiple pathways and activities/intake rates associated with multiple chemicals.
Sociodemographic Data Used for Identifying Potentially Highly Exposed Populations (U.S. EPA) http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=22562	Fact Finder searches and returns data from the Sociodemographic Data Used for Identifying Potentially Highly Exposed Populations document. These data assist assessors in identifying and enumerating potentially highly exposed populations. Due to unique social and demographic characteristics, various segments of the population may experience exposures different from those of the general population, which in many cases could be higher. It is helpful for risk or exposure assessors evaluating a diverse population to first identify and then characterize certain groups within the general population who could be at risk for greater contaminant exposures (and related effects).	This document presents data relating to factors which potentially impact an individual or group's exposure to environmental contaminants based on various activity patterns, different microenvironments, and other socio-demographic data such as age, gender, race and economic status. Populations potentially more exposed to multiple chemicals of concern, relative to the general population, is also addressed in this database.

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TABLE A-3 cont.		
Resource and Access	Purpose and Scope	Cumulative Risk Remarks
3MRA (U.S. EPA) http://www.epa.gov/ceampubl/mmedia/3mra/index.htm (CEAM)	Developed for screening-level assessment of potential human and ecological health risks from chronic exposures to chemicals released from land-based waste management units containing listed waste streams. Site-based and intended for national-scale application to generate risk-based standards (e.g., levels to exit from hazardous waste regulation), evaluates human and ecological receptors, and captures uncertainty and variability in risk estimates. (Ecological exposure and risk focuses on population effects related to key species within habitats found in the proximity of sites.)	Can quantify exposure via multiple pathways after a simulated release. Human receptors include adult/child residents, home gardeners, beef and dairy farmers, and recreational fishers. Pathways include inhalation of outdoor air and indoor air during showering, ingestion of drinking water, and ingestion of farming products and fish.
E-FAST (U.S. EPA) http://www.epa.gov/opptintr/exposure/docs/efast.htm	Provides screening-level estimates for general population, consumer, and environmental exposures to concentrations of chemicals released to air, surface water, landfills, and from consumer products. Modeled estimates of concentrations and doses are designed to reasonably overestimate exposures, for use in screening-level assessments.	Default exposure parameters are available, but site-specific values are recommended to be used. Can predict exposure concentrations for comparison to media-specific standards.
All Ages Lead Model (U.S. EPA): http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=139314	Predicts lead concentrations in body tissue and organs for a hypothetical individual based on a simulated lifetime of lead exposure, and then extrapolates to a population of similarly exposed individuals.	Useful for evaluating the impact of possible sources of lead in a specific human setting where there is a concern for potential or real exposures to lead. The results can be correlated with risks from other contaminants, if interactions with lead are known to occur.

TABLE A-3 cont.		
Resource and Access	Purpose and Scope	Cumulative Risk Remarks
CALTOX Model (CalEPA)	Spreadsheet-based model that relates the concentration of a chemical in soil to the risk of an adverse health effect for a person living or working on or near a site. Determines chemical concentration in the exposure media of breathing zone air, drinking water, food, and soil that people inhale, ingest and contact dermally, and uses the standard equations found in U.S. EPA RAGS (U.S. EPA, 1989a) to estimate exposure and risk.	Can be used to assess multiple exposures; has tended to be more for research than practical applications. Defaults are available but site-specific values are recommended. Can predict exposure concentrations that can be compared to media-specific standards and used to estimate single-chemical risks.
Dietary Exposure Potential Model (DPEM) (U.S. EPA) http://www.epa.gov/nerlcww/depm.htm	The DEPM estimates dietary exposures to multiple chemicals based on data from several national, government-sponsored food intake surveys and chemical residue monitoring programs.	Can be used to assess exposures to multiple chemicals by ingestion of food and tap water, including as potential context for ambient exposures in the area of a site.
Disease registries (multiple organizations, including CDC:) http://www.cdc.gov/cancer/natlcancerdata.htm	A number of databases exist for cancer and other health-related information, such as asthma and birth defects.	Data could be used to indicate key community health concerns or for exploratory investigation of certain diseases that might increase the vulnerability of certain people exposed to chemicals from a contaminated site. However, the links to diseases from environmental exposures or directly to environmental pollutants as a causal or contributing factor is not usually clear.

TABLE A-3 cont.		
Resource and Access	Purpose and Scope	Cumulative Risk Remarks
Tool for the Reduction and Assessment of Chemical and Other Impacts (TRACI) (U.S. EPA) http://www.epa.gov/ordntrnt/ORD/NRMRL/pubs/600r02052/600r02052.htm	TRACI is an impact assessment tool for evaluating multiple chemical impact and resource-use categories so various study designs can be analyzed.	Can be used to model and compare exposures to multiple chemicals and health risks associated with different projects. For example, can graphically analyze the reduction in risk projected from one implementation design versus another.
NORA Mixed Exposures Team (NIOSH) http://www2a.cdc.gov/nora/noratopictemp.asp?rscharea=me	Provides technical and support information on projects involving mixed exposures in the workplace. Research reflected on the website could provide insights for cumulative risk assessment projects.	Information resource for mixtures in the workplace; can offer insights for cumulative assessments at contaminated sites.

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A.4. RESOURCES FOR TOXICITY ANALYSES

Resources that can be used to support toxicity analyses for cumulative risk assessments are highlighted below and summarized in Table A-4. Topics include: (1) development of toxicity factors, including for whole mixtures; (2) identification of toxicity criteria for similar or surrogate compounds or mixtures to represent a mixture or its components; and (3) joint toxicity of the components of a mixture.

- **Integrated Risk Information System, IRIS (U.S. EPA).** The IRIS database is a key source of information on chronic toxicity, including standard toxicity values (reference doses and concentrations), cancer slope factors, and corresponding risk-based concentrations. These values have undergone thorough Agency review and represent expert Agency consensus, and they are widely used within the United States and by other countries. Toxicity values and target tissue information included in IRIS summaries can be used in a cumulative risk assessment to identify chemicals that primarily or secondarily affect similar target tissues or systems. Chemical interactions other than addition are not quantifiable using toxicity criteria from IRIS; however, information in the accompanying study summaries can be used to qualitatively assess the nature and magnitude of certain interactions, and the primary literature can be further pursued for additional information. Toxicity criteria are presented in a way that supports addition (the default approach) to estimate risks and the potential noncancer effects of chemicals. This information is available at http://www.epa.gov/iris/.

- **Toxicological Profiles and Interaction Profiles (ATSDR).** The ATSDR, within the U.S. Centers for Disease Control and Prevention (CDC), has developed toxicological profiles for many individual chemicals that summarize information about sources and uses as well as key data from the scientific literature regarding toxicity and behavior and levels in the environment. These profiles can be valuable for cumulative risk assessments because they describe in detail the effects of the given chemical, as well as its primary environmental and metabolic transformation products, on specific target organs and biological functions. In addition, where possible, the toxicological profiles discuss known interactions of the topic chemical with other chemicals. These profiles are available at http://www.atsdr.cdc.gov/toxpro2.html.

  The ATSDR has also developed a mixtures program and has drafted a guidance manual that presents an assessment approach, and perhaps more importantly has drafted nine interaction profiles for seven specific chemical combinations and two general mixtures. The specific chemical combinations are: (1) arsenic, cadmium, chromium, and lead; (2) benzene, toluene, ethylbenzene, and xylene; (3) lead, manganese, zinc, and copper; (4) cyanide, fluoride, nitrate, and

uranium; (5) cesium, cobalt, PCBs, strontium, and trichloroethylene; (6) 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene; and (7) arsenic, hydrazine, jet fuels, strontium-90, and trichloroethylene. These interaction profiles evaluate data on the toxicology of the whole mixture where available, and where not available data are evaluated for the joint toxicity of chemicals in the mixture (often as pairs). These drafts are available at http://www.atsdr.cdc.gov/iphome.html.

- **Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures (U.S. EPA).** This guidance published in summer 2000 updates the Agency's 1986 guidelines for chemical mixtures (U.S. EPA, 2000a). It describes approaches that depend on the type, nature, and quality of available data. The report includes equations, definitions, discussions of toxicologic interactions and pharmacokinetic models, and approaches for assessing whole mixtures, surrogate mixtures, and individual mixture components. The whole-mixture discussion includes the whole-mixture reference dose (RfD) and concentration (RfC) and slope factors; comparative potency; and environmental transformations. The component discussion includes the hazard index (HI); interaction-based HI; relative potency factors (RPF); and response addition. Toxicity criteria are presented for several common product mixtures, such as polychlorinated biphenyls (PCBs). This guidance is available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20533.

- **Database for Airborne Workplace Chemicals (Institut de Recherche Robert-Sauve en Santé et en Sécurité du Travail, IRSST).** This health and safety research institute in Quebec, Canada, has developed a database that covers a large number of chemicals commonly found in the workplace, and also found at many contaminated sites. This database contains information on occupational standards, chemical-specific health effects, target organs (and chemical-specific groupings), toxicokinetics, effect levels, and mode of action where available. The database also includes a calculation tool that allows up to 10 chemicals to be assessed at a time, comparing the concentration of interest to the occupational standard (many are similar to ours) to produce a sum of ratios, using an additivity default (IRRST, 2003).

- **Relative Potency Factors for Pesticide Mixtures, Biostatistical Analyses of Joint Dose Response (U.S. EPA).** In response to requirements of the Food Quality Protection Act of 1996, U.S. EPA recently published a technical report that presents research and methodologies for developing relative potency factors by which cumulative risks from exposures to mixtures such as organophosphate pesticides, dioxins, and PCBs can be assessed (U.S. EPA, 2003f). The document presents three scenarios for which biostatistical methods for toxicity assessment can be accomplished, including use of dose addition in simple cases where common modes of toxicity are present, integration of dose and response addition for cases where toxicities are independent, and joint dose-response modeling for cases where the mode of action is uncertain. The report, published

by NCEA in coordination with OPP, is available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=66273.

- **Cumulative Risk of Pesticides with Common Toxic Mechanism (U.S. EPA).** In response to the Food Quality Protection Act, the U.S. EPA Office of Pesticide Programs (OPP) recently released an assessment of the risks associated with cumulative exposures to various formulations of organophosphate (OP) pesticides (U.S. EPA, 2002a). This report updated the preliminary assessment released a year earlier. For this assessment, the Agency evaluated potential exposures to 30 OPs, including via food, drinking water and residential uses, and applied methodologies to account for variability in exposures based on age, seasonal, and geographic factors. The cumulative risk assessment report is available at http://www.epa.gov/pesticides/cumulative/rra-op/.

- **Dose Addition for Cumulative Risks from Exposures to Multiple Chemicals (U.S. EPA).** As part of the response to the Food Quality Protection Act of 1996, which requires consideration of cumulative risk from exposures to multiple chemicals that have a common mechanism of toxicity, NCEA published a paper describing three dose addition-based techniques that can be used to estimate cumulative risk (Chen et al., 2001). The three methods include the hazard index (HI), point-of-departure index (PODI), and toxicity equivalence factor (TEF), all of which are based on estimates of a point of departure (as the effective dose for a 10 percent response, or ED10) and reference doses of individual chemicals. A formal statistical procedure is also proposed to estimate cumulative risk by fitting the dose-response model of the mixture under dose addition and estimating relative potency between two chemicals from that model.

- **Long-Range Research Initiative, LRI (American Chemistry Council, ACC).** Through its LRI program, the ACC sponsors scientific research aimed at better understanding the potential impacts of chemicals on human health and the environment, including wildlife (ACS, 2003). Cumulative risk is a priority research area within the LRI program, and studies are ongoing. Reports and papers prepared from this research can provide insights for cumulative risk assessments at contaminated sites. Research topics include improved methods for understanding toxicodynamics, applications of physiologically-based pharmacokinetic (PBPK) models to predict target tissue dose and response, and exposure assessment of mixtures. The LRI holds a conference each year at which ongoing and completed research is presented. The summary report of the recent annual conference, with abstracts of research projects presented, can be found at http://www.uslri.com/.

- **Chemical Mixtures Toxicology Studies (Netherlands, TNO).** International research is currently underway to improve the understanding of potential risks of chemical mixtures with different modes of action. For example, a team led by Dr. John Groten of the TNO Nutrition and Food Research Institute of the Netherlands is researching the use of mechanistic models to describe interactions between

mixture components expected to act by different modes of action. In an ongoing pilot study (funded by ACC/LRI), the TNO team is using PBPK models to assess possible toxicokinetic interactions between compounds in an applied mixture, and comparing them to empirical dose-response modeling of observed pathological changes in liver, blood and kidney. The aim is to apply the method developed to other chemical mixtures. Other studies have developed and applied statistical experiments combining multivariate data analysis and modeling in *in vitro* and *in vivo* studies on various chemical mixtures such as petroleum hydrocarbons, aldehydes, food contaminants, industrial solvents, and mycotoxins (Feron et al., 1998).

- **Scientific Studies on Toxicology/Mixtures (National Institute of Environmental Health Sciences, NIEHS).** Research areas of the NIEHS, within the National Institutes of Health (NIH), U.S. Department of Health and Human Services (DHHS), include toxicology, mixtures, and environmental health. The Institute sponsors the National Toxicology Program (NTP), which coordinates toxicological testing programs; strengthens the science base in toxicology; develops and validates improved testing methods; and provides information about potentially toxic chemicals to health regulatory and research agencies, scientific and medical communities, and the public. Fact sheets and reports on chemicals and related risks, and data and findings from NTP-related studies are available at http://www.niehs.nih.gov/. This website also links to other research projects and programs within the organizationand summaries of past and ongoing studies that can provide insights for cumulative risk assessments at contaminated sites. A search engine on the website can be used to identify research and tools for specific applications, including those related to cumulative risk. NIEHS also publishes *Environmental Health Perspectives*, a monthly journal that often summarizes research papers relevant to chemical mixtures, and some issues and supplements have been entirely dedicated to mixtures. Also, NIH maintains the National Library of Medicine Toxic Substances Data Bank and other valuable databases and biomedical links.

- **Toxic Substances Research Initiative, TSRI (Health Canada).** The Canadian environmental health department (Health Canada) has developed a program called the Toxic Substances Research Initiative (TSRI). The primary focus of this initiative is assessment of cumulative effects to human and ecological receptors. To date, TSRI has spent more $7 million to fund 23 research projects in this priority research area. Resulting technical reports and other publications are available at http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/2000/2000_69bk2_e.html. One example research study is the evaluation of the pharmacokinetics and cumulative health effects of mixtures of disinfection byproducts, led by Dr. Kannan Krishnan of the University of Montreal.

- **Toxicity Values for Diesel Particulate Matter (DPM) Mixture (California EPA).** Risks of whole mixtures are evaluated using toxicity criteria developed for that mixture where data are available. In 1998, the CalEPA Office of Environmental

Health Hazard Assessment (OEHHA) completed a 10-year human health assessment of the mix of chemicals in diesel exhaust. From the results the California Air Resources Board (CARB) identified diesel particulate matter (DPM) exhaust as a toxic air contaminant (TAC) that poses a threat to human health. This exhaust results from combustion of diesel fuel in internal combustion engines. Its composition varies based on engine type, operating conditions, fuel composition, lubricating oil, and whether an emission control system is present. The DPM exhaust is a complex mixture of thousands of fine particles, commonly known as soot; this contains 47 compounds classified by U.S. EPA as hazardous air pollutants (HAPs) and by CARB as TACs. These compounds include many known or suspected carcinogens, such as benzene, arsenic, formaldehyde, and nickel. The CARB evaluation exhaust takes into account its individual components; chemicals commonly found in diesel exhaust are shown in Text Box A-1.

Toxic Air Contaminants in Diesel Exhaust*
(Text Box A-1)

Acetaldehyde
Acrolein
Aluminum
Ammonia
Aniline
Antimony compounds
Arsenic
Barium
Benzene
Beryllium compounds
Biphenyl
Bis [2-ethylhexyl]phthalate
Bromine
1,3-Butadiene
Cadmium
Chlorinated dioxins
Chlorine
Chlorobenzene
Chromium
Cobalt compounds
Copper
Cresol
Cyanide compounds
Dibenzofuran
Dibutylphthalate
Ethyl benzene
Formaldehyde
Hexane
Lead compounds
Manganese compounds
Mercury compounds
Methanol
Methyl ethyl ketone
Naphthalene
Nickel compounds
4-Nitrobiphenyl
Phenol
Phosphorus
Polycyclic aromatic hydrocarbons
Propionaldehyde
Selenium compounds
Silver
Styrene
Sulfuric acid
Toluene
Xylene isomers and mixtures
Zinc

*These have either been identified in diesel exhaust or are presumed to be in the exhaust based on observed chemical reactions and/or their presence in the fuel or oil. Additional information at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=29060.

The report prepared from the CARB assessment *Proposed Identification of Diesel Exhaust as a Toxic Air Contaminant* was formally reviewed and approved by a scientific review panel. The panel deemed data from human epidemiological studies of occupationally exposed populations to be applicable for quantitative risk assessment. After considering the results of the meta-analysis of human studies, as well as the detailed analysis of railroad workers, the panel developed a unit risk estimate expressed in terms of diesel particulates, which was then used to derive an inhalation slope factor of 1.1 $(mg/kg\text{-}day)^{-1}$. This type

of approach might offer useful insights not only for assessments involving diesel exhaust but also for assessments at sites with other chemical mixtures.

- **Toxicity/Risk Technical Resource (U.S. EPA National Center for Environmental Assessment, NCEA).** As a major research center within the U.S. EPA Office of Research and Development (ORD), NCEA serves as the Agency's national resource for human health and ecological risk assessment. The Center conducts risk assessments as well as research to improve the state-of-the-science, and also provides guidance and technical support to risk assessors. This organization manages and is responsible for updating the content of the IRIS database (U.S. EPA, 2005c). Risk assessors can contact NCEA for help regarding provisional values when toxicity values are not available in IRIS. Information available online at http://cfpub.epa.gov/ncea/ can offer useful insights for cumulative risk assessments. Ongoing research is being conducted by NCEA in the development of PBPK models for use in risk assessments, the evaluation of different risk assessment approaches, the modified hazard index approach for chemical mixtures assessments, and the significance of indirect exposure pathways and quantitative models of variability for assessing uncertainty.

- **Statistical/Computer Tools in Development (Universities, Research Institutes).** Statistically based methods and computer tools that can model interactions and effects associated with multiple chemicals are being developed. A main area of study involves applying physiologically based pharmacokinetic/ pharmacodynamic (PB-PK/PD) models to chemical mixtures. Many researchers are working in this area (e.g., M. Anderson, K. Krishnan, and R. Yang), and advances continue to be made. An example of a computer-based approach for predicting toxicological interactions of chemical mixtures is reaction network modeling, which has been to model complex chemical processes in petroleum engineering. For this effort, reaction network modeling incorporates various statistical methods (including Monte Carlo-type analysis) to predict chemical reaction rates, products, and outcomes. A molecular-based model (BioMOL) is in development, which uses this reaction network modeling approach to predict effects of chemicals in complex biological systems (Liao et al., 2002).

- **BMDS (U.S. EPA).** This software was developed by U.S. EPA to perform fitting of mathematical models to toxicological dose-response data for a particular toxic effect (U.S. EPA, 1995c). The user evaluates the results to select a benchmark dose (BMD) that is associated with a predetermined benchmark response (BMR), such as a10% increase in the incidence of a particular lesion or a 10% decrease in body weight gain. A goal of the BMD approach is to define a starting point of departure for the computation of a reference value (RfD or RfC) or slope factor that is more independent of study design than the traditional method that uses a single experimental dose, such as the no-observed-adverse-effect level (NOAEL). The hazard index uses RfDs or RfCs in a dose addition formula to scale the exposure levels in a mixture, producing an indicator of the extent of

concern for toxicity. The BMD values used with dose addition could allow estimation of a BMD for the mixture, allowing the mixture dose to be interpreted in terms of the risk of a particular effect.

- **CatReg (U.S. EPA).** This categorical regression tool was developed by U.S. EPA to conduct meta-analyses of toxicological data, i.e., to analyze data or results from multiple studies including to assess different severity levels. The tool is a customized software package that runs under S-PLUS (MathSoft, Inc.), and a free version written in R is under development. Additional context is offered as follows (from U.S. EPA, 2000c): "Meta-analysis becomes valuable when individual experiments are too narrow to address broad concerns. For example, in acute inhalation risk assessment, it is important to investigate the combined effects of concentration and duration of exposure but few published experiments vary both the concentration and the duration of exposure. By combining information from multiple studies, the contribution of both concentration and duration to toxicity can be estimated. Moreover, the combined analysis allows the analyst to investigate variation among experiments, an important benchmark for the level of model uncertainty." For cumulative health risk assessments, CatReg can be applied to evaluate grouped chemicals considering multiple effects and multiple routes. Also, during the validation of CatReg, Sciences International (under contract to NCEA) developed three acute values; that product was submitted for consideration in adding to the IRIS database. Therefore, this tool can also be used to support toxicity values.

- **Risk-Based Screening Levels (U.S. EPA).** Risk-based screening criteria have been developed for environmental media (including soil, drinking water, and air) by several organizations. For example, U.S. EPA Regions 3, 6, and 9 have developed risk-based concentrations (RBCs), medium-specific screening levels (MSSLs), and preliminary remediation goals (PRGs), respectively. These screening values are based on very conservative default assumptions for exposure and environmental parameters and incorporate toxicity values for cancer and non-cancer effects from IRIS, PPRTV, and the old Health Effects Assessment Summary Tables (HEAST), which have not been updated since 1997. Information for the MSSLs is presented in technical guidance (U.S. EPA, 2005e) and can be found at http://www.epa.gov/earth1r6/6pd/rcra_c/pd-n/r6screenbackground.pdf. The PRGs developed from the guidance (U.S. EPA, 2002g) can be found at http://www.epa.gov/region09/waste/sfund/prg/files/02userguide.pdf. The RBCs are described in a technical memorandum (U.S. EPA, 2003i) and can be found at http://www.epa.gov/reg3hwmd/risk/human/info/cover.htm. These screening criteria can be used to narrow the focus of the assessment to those chemicals of potential concern likely to contribute the most to overall risks associated with the site. However, the screening values do not reflect site-specific exposure routes and are of limited usefulness for site-specific cumulative risk assessments because they do not consider relevant setting and exposure information.

TABLE A-4

Selected Resources for Evaluating Joint Toxicity

Resource and Access	Purpose and Scope	Cumulative Risk Remarks
Integrated Risk Information System (IRIS) (U.S. EPA) http://www.epa.gov/iris	An electronic database containing information on human health effects that may result from exposure to various chemicals in the environment. Describes toxic effects, dose concentrations, and reference inhalation dose concentrations for oral and inhalation exposures of over 500 chemicals. Good resource for identifying individual toxicological effects for an extensive list of chemicals. Combined with specific exposure information, the data in IRIS can be used for characterization of the health risks of a given chemical in a given situation and provide toxic effects of a particular chemical within a chemical mixture.	Toxicity values and target organ information included in IRIS summaries can be used in cumulative risk assessments to identify chemicals that primarily or secondarily affect similar target tissues or systems. Chemical interactions other than addition are not quantifiable using these toxicity criteria; however, the nature(s) and magnitudes of some interactions could be predicted. Toxicity criteria are calibrated such that health effects and cancer risks can be readily summed where effects are assumed to be additive.
Technical resource (U.S. EPA) http://www.epa.gov/ncea	NCEA is a technical resource for many topics relevant to cumulative assessments. These U.S. EPA scientists provide guidance and support to risk assessors across a broad scope of assessment issues, including cumulative health risk.	Serves as the source of provisional toxicity values (where standard toxicity values are not available) and related data.
Interaction profiles (draft) (ATSDR) http://www.atsdr.cdc.gov/iphome.html	These interaction profiles summarize available toxicity data for mixtures and assesses joint toxicity. Drafts exist for nine combinations (see accompanying text). Information includes critical effect levels and directions of interactions with confidence indicators by organ/system, and also includes representative chemicals	Useful for assessing cumulative risks when exposures involve chemicals covered in the profiles. Good resource for finding specific toxicity data organized by organ/system to determine at what levels joint toxicity could be exerted among chemical sets without having to search in the primary literature. Some secondary effects information is included.

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TABLE A-4 cont.		
Resource and Access	Purpose and Scope	Cumulative Risk Remarks
Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures (U.S. EPA) http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20533	This guidance presents approaches for assessing risks of mixtures, as dictated by the nature and quality of available data (e.g., for mixtures, surrogate mixtures, or individual mixture components). Provides formulas, definitions, and discussions of toxic interactions and pharmacokinetic models. (Does not address exposures, just toxicity.)	Presents more detailed information on considerations and calculational approaches for assessing mixtures, going beyond the summaries included in Chapters 5 and 6 of this report.
TOXNET, other databases (NIH) http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB	NIH sponsors many databases for toxicology and environmental health, including TOXNET and Haz-Map (hazardous chemicals and occupational disease), and MEDLINE links to biomedical journals.	Useful source of single-chemical information, will also reflect emerging data relevant to cumulative risks as they are developed.
Chemical database (IRSST) http://www.irsst.qc.ca/fr/_outil_100015.html	Database for airborne chemicals in the workplace that includes the Canadian occupational standards (many are the same as U.S. standards) and identifies target organs, effect levels from toxicity studies, and, where available, mode of action information; includes a sum-of-ratios tool to assess airborne chemicals compared to standards, for up to 10 at a time. (The database is in French; it is currently being translated to English.)	Good source of useful inhalation toxicity information for a large number of chemicals. The tool can be used to organize chemicals by target organ/effect and levels can be ratioed to a reference level (occupational standard), with an option for calculating a sum of ratios for 10 chemicals at a time (assumes additivity) for a combined estimate.
Revised Cumulative Risk Assessment of Pesticides That Have a Common Mechanism of Toxicity (U.S. EPA) http://www.epa.gov/pesticides/cumulative/rra-op	Identifies methods, review toxicities, develop relative potency factors and present risks associated with cumulative exposures to organophosphate pesticides. Document reviewed toxicity, product, and exposure data for 30 organophosphate and presented detailed findings on cumulative risks.	One of the first comprehensive risk assessments addressing cumulative risk; offers good insights for multipathway assessments.

TABLE A-4 cont.

Resource and Access	Purpose and Scope	Cumulative Risk Remarks
Studies within Long-Range Research Initiative (LRI) (ACC) http://www.uslri.org/	Industry-funded scientific program includes a cumulative risk focus area. Ongoing research in this area is addressing assessment methods and toxicity studies for mixtures.	Research results could offer insights for cumulative risk assessments at contaminated sites.
BMDS (U.S. EPA) http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20167	BMDS is designed to fit mathematical models to dose-response data so that the results allow selection of a benchmark dose (BMD) that is associated with a predetermined benchmark response (BMR), such as a 10% increase in the incidence of a particular lesion or a 10% decrease in body weight gain. General guidance is available. Technical guidance document for BMDS is available online (external review draft). Periodic revision.	BMD values used with dose addition could allow estimation of a BMD for the mixture. For toxicity endpoints usually described by virtually safe levels (RfDs and RfCs), this approach would provide a risk-based dose associated with risk of a particular effect.
CatReg (U.S. EPA) http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=181622	Categorical regression model developed for meta-analysis of toxicology data. Still in development, this could be useful for evaluating different types of data in evaluating potential cumulative health risks.	CatReg can be used to evaluate multiple effects within a chemical grouping (e.g., as grouped by target organ or system) and can also be used as a tool to support the health effect estimate (e.g., hazard index) from multiple-route exposures.
Risk-based screening levels (see text, can be found through: http://www.epa.gov/region09/waste/sfund/prg/, http://www.epa.gov/reg3hwmd/risk/eco, and http://epa.gov/earth1r6/6pd/rcra_c/pd-n/screen.htm	Screening criteria for environmental media (soil, drinking water, and air) based on specified risk levels, based on conservative assumptions and extant toxicity values (some are outdated); developed by various U.S. EPA regions, offices, and other organizations. For example, U.S. EPA Regions 3, 6, and 9 have developed risk-based concentrations (RBCs), medium-specific screening levels (MSSLs), and preliminary remediation goals (PRGs), respectively.	Not designed for cumulative risk assessment, because they are chemical-specific and not based on specific pathways or target organs. However, they could be useful for narrowing the assessment focus (e.g., during data evaluation) to those chemicals most likely to contribute to overall risks at a site.

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A.5. RESOURCES TO CHARACTERIZE RISK AND UNCERTAINTY AND PRESENT RESULTS

Many assumptions are made when assessing human health risks of multiple chemicals from environmental exposures. Thus, it is important for the risk results and associated uncertainties to be well characterized and clearly presented so this information can be appropriately interpreted to guide sound decisions. This can involve graphical illustrations of statistical and spatial information, as highlighted below. Selected tools to support this final phase of the cumulative risk assessment are summarized in Table A-5.

- **Spatial Analysis and Decision Assistance (SADA) (U.S. EPA and U.S. Nuclear Regulatory Commission, NRC).** The NRC joined U.S. EPA to support a very useful integrated software package to support human and ecological cumulative risk assessments, working with the University of Tennessee. The human health module of this tool includes the equations from the standard Superfund guidance (U.S. EPA, 1989a) and contains flexible land use scenarios and exposure pathways. These can be combined as indicated to represent overall exposure for the representative receptors evaluated. The input data for these pathways can be tailored to reflect site-specific conditions; interactions are not considered. This tool emphasizes the spatial distribution of contaminant data, and modules cover visualization, geospatial analysis, statistical analysis, sampling design, and decision analysis. Outputs can be tabular or graphical, and can be used to identify where risk results exceeds a target value. Many SADA capabilities are also covered by the Fully Integrated Environmental Location Decision Support (FIELDS) system, which is coordinated through U.S. EPA Region 5 and accessible from ArcView. The SADA tool is available at http://www.tiem.utk.edu/~sada/.

- **Probabilistic Resources (U.S. EPA, Others).** Risk assessments commonly present human health risks as single-point estimates (e.g., 1×10^{-5}), following U.S. EPA's basic risk assessment guidance for contaminated sites (U.S. EPA, 1989a). Such estimates provide little information about the underlying uncertainty or variability. The uncertainty typically spans at least an order of magnitude and often much more. Monte Carlo simulation offers one way of considering uncertainty and variability, as it relies on multiple descriptors using statistical techniques to calculate a quantity repeatedly with inputs selected randomly from a reasonable population of values (U.S. EPA, 1999i). Results approximate a full range of reasonably possible outcomes and are typically plotted as graphs (e.g., frequency distributions) or tabulated. However, this

approach has several limitations, which affect its acceptance as a preferred assessment method. Limitations include: difficulty in distinguishing between variability and uncertainty; use of exposure parameters developed from short-term studies for long-term exposure; and sensitivity of the tails of the distributions, which can be of greatest interest, to input distributions. Nevertheless, Monte Carlo simulation approaches offer one way to represent uncertainty and variability in the risk results.

- **RESRAD (DOE Argonne National Laboratory).** The original RESidual RADioactivity code was designed to evaluate radiological risks and develop radiological cleanup levels. It can cover 14 combined exposure pathways and is used by DOE for radioactively contaminated sites and by NRC for dose evaluations to support decommissioning and waste disposal requests. Subsequent additions to the family of codes include RESRAD-CHEM (which calculates risks and hazard indices across 9 exposure pathways and includes a database of chemical properties, transfer factors, and toxicity values for about 150 chemicals), RESRAD-BASELINE (which covers both radionuclides and chemicals and uses measured concentrations as input), and RESRAD-OFFSITE (with includes a two-dimensional dispersion groundwater model and the CAP-88PC air dispersion model). Outputs can be tabular and graphic, and the code includes a Monte Carlo module for probabilistic analyses. The code incorporates transformation over time for radioactive decay, but like many others it does not address environmental transformation of chemicals or interactions.

- **Regional Air Modeling Initiative (RAIMI) (U.S. EPA).** The Regional Air Modeling Initiative (RAIMI) approach developed by U.S. EPA Region 6 is GIS-based and looks at multiple sources across U.S. EPA programs. This tool was developed by Region 6 and uses multiple emissions data sources to assess community-level inhalation impact by evaluating an unlimited number of stationary and mobile air toxics sources. It utilizes both air and risk modeling components. RAIMI also supports source attribution analyses, so individual sources can be for targeted reductions rather than simply revealing areas of concern. Initial findings indicate that a small number of sources may be responsible for the majority of impact. Such models aim to become useful beyond Region 6, as U.S. EPA moves to risk-based approaches across all programs. In the RAIMI approach, cumulative information does not necessarily take into account the effect of complex mixtures, as additivity is assumed. At a July 2003 meeting of the Advisory Board, several potential applications of this tool were identified, including using the RAIMI dataset in conjunction with the cumulative risk framework; predicting future risk, or the impact of past regulation; or integrating data sources. The tool is already being used to identify useful databases and emissions inventories. The model has been submitted to the U.S. EPA's Council for Regulatory Environmental Modeling (CREM) for validation. The tool currently focuses on one medium (air) so it would need to link with other modules to address other sources of risk (such as from community drinking water

or food residues) for a full cumulative assessment. Information is available at http://www.epa.gov/earth1r6/6pd/rcra_c/raimi/raimi.htm.

- **Cumulative Risk Index Analysis (U.S. EPA).** The Cumulative Risk Index Analysis (CRIA) System is a multi-purpose environmental assessment tool based on GIS technology from U.S. EPA Region 6. This GIS-based screening system uses data from major government databases and inputs from technical and regulatory professionals to mathematically transform information relevant to cumulative risk to visual forms such as GIS maps and tables. The system has been used to assess and display human health, ecological, socio-economic and regulatory risk information. The framework developed for implementing CRIA is available from the U.S. EPA website at http://www.epa.gov/osp/presentations/cumrisk/carney.pdf. Region 6 has conducted over 6,500 cumulative risk assessments in environmental justice communities using its Comparative Cumulative Risk System.

- **Other GIS Tools (Private).** Several government agencies and private companies have developed GIS programs to simultaneously assess exposures of multiple chemicals by a single receptor. For example, ESRI, Inc., has developed the screening-level risk assessment module RISKMOD for its ArcView platform; this tool calculates cumulative risks from multiple contaminants. For carcinogens, risk is calculated for each exposure pathway by summing the individual lifetime excess cancer risks for each chemical associated with that pathway. For non-carcinogens, the hazard quotients for each exposure pathway can be summed to produce a hazard index for that pathway (Naranjo et al., 2000). A case study illustrating how RISKMOD was applied to assess risks for a Bolivian mine site is available at http://gis.esri.com/library/userconf/proc00/professional/papers/PAP480/p480.htm.

- **Cumulative Adjustment of Protective Concentration Levels (PCLs) (Texas, TCEQ).** PCLs are a set of toxicity-based screening criteria developed by TCEQ for use in risk assessments of sites in the state. Whereas the individual PCLs were derived for evaluation of risks from individual chemicals, the TCEQ has developed an equation for downward adjustment of the PCLs for use when evaluating risks where at least 10 carcinogenic or noncarcinogenic chemicals of concern (COC) are present for a specific exposure pathway. The adjustments result in reduced PCLs for individual chemicals based on the ratio of the measured concentration of each COC to its PCL. If the sum of these ratios exceeds a predetermined value (here, 10), adjusted PCL values may be necessary for some COCs to ensure that state risk reduction rule mandates are met (i.e., cumulative cancer risks for multiple carcinogenic COCs cannot exceed 1×10^{-4}, and the hazard index for multiple noncarcinogenic COCs cannot exceed 10). The COCs to be adjusted are determined based on a decision process outlined in the Cumulative Adjustment guidance document (TCEQ, 2002). The adjustment process is a simplistic budgeting exercise in which the risk assessor

is able to choose the PCLs to be lowered and the magnitude of the reduction. The guidance document is available at http://www.tceq.state.tx.us/.

- **Framework for Risk Analysis in Multimedia Environmental Systems (FRAMES) (U.S. EPA).** The U.S. EPA has developed an integrated software system with support from Pacific Northwest National Laboratory, to conduct screening-level assessments of health and ecological risks for hazardous waste identification rule (HWIR) chemicals from land-based waste management units.

TABLE A-5

Selected Resources for Characterizing Risk and Uncertainty and Presenting Results

Resource and Access	Purpose and Scope	Cumulative Risk Remarks
SADA (Spatial Analysis and Decision Assistance) (DOE, NRC, UT) http://www.tiem.utk.edu/~sada/	Integrated set of software with flexible land use scenarios and exposure pathways to assess health risks. The tool emphasizes spatial distribution of contaminant data; modules cover visualization, geospatial analysis, statistical analysis, sampling design, and decision analysis. Outputs can be tabular or graphical. (Also covers ecological risks, aims to support integrated decisions.)	Useful for cumulative risk assessments; can combine pathways to assess overall exposures and summed risks/hazard indices for receptors of interest. Input data can reflect site-specific conditions; interactions are not considered.
RESRAD (RESidual RADioactivity) (DOE-ANL) http://www.ead.anl.gov/resrad (family of codes, including RESRAD-CHEM and BASELINE for chemicals)	The original code was designed to guide radiological cleanup criteria for contaminated sites and assess doses and risks from residual radionuclides. Sister codes cover chemical contaminants to support a combined evaluation of risks and hazard indices at sites with radionuclides and chemicals. Includes a screening groundwater model, links to an air dispersion model, and includes a probabilistic module. Outputs are graphics and tables.	Useful for cumulative assessments at radioactively and chemically contaminated sites; can assess sensitivity, covers natural radioactive decay (but not environmental transformation) to address changes over time; produces risk and hazard indices summed across multiple contaminants and pathways; does not address interactions.
Monte Carlo Analysis-Based Resources (U.S. EPA, others)	Statistical methods for addressing uncertainty and variability in estimating health risks by developing multiple descriptors to calculate a quantity repeatedly with randomly selected scenarios for each calculation. Most useful for single-point risk estimates; can be a useful as a presentation tool because graphics show range of scenarios and outputs.	Combining approximations for multiple sources of potential risk (e.g., environmental and lifestyle risk) can be complicated. Could be used to evaluate cumulative risks by combining results for individual exposures that consider variability and uncertainty.

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TABLE A-5 cont.

Resource and Access	Purpose and Scope	Cumulative Risk Remarks
Regional Air Impact Modeling Initiative (RAIMI) (U.S. EPA) http://cfpub2.epa.gov/crem/crem_report.cfm?deid=74913	Risk-based prioritization tool developed by Region 6 to support regional risk-based prioritization at a community-level resolution, from exposures to multiple airborne contaminants from multiple sources via multiple exposure pathways. Designed to support cross-program analyses. Includes Risk-MAP, to estimate health risks from exposures to chemical emissions over large areas.	Assesses multiple contaminants and multiple sources for U.S. EPA programs, for air contaminants. Designed to consider source-specific and contaminant-specific contributions to cumulative exposures associated with the air pathway.
Cumulative Risk Index Analysis (CRIA) (U.S. EPA) http://www.epa.gov/osp/presentations/cumrisk/carney.pdf	Analyze and present cumulative risks spatially and statistically using a GIS-based tool designed by U.S. EPA Region 6. Useful for projects where quality toxicity, geographical, and exposure data exist. Useful for cumulative impacts analysis in National Environmental Policy Act (NEPA) projects, including ecological stressors and sources of pollutants impacting humans.	Designed specifically for spatial presentation of cumulative risks. Can compare human health and ecological risks. 90 environmental criteria are in use, with 45 used to identify multimedia inspection targets. Also considers cultural resource concerns and sensitive subpopulations.
Environmental Load Profile (U.S. EPA) http://www.epa.gov/region02/community/ej/guidelines.htm#step4	Compares indicators of well-being with statewide-derived benchmarks. A screening-level tool developed by U.S. EPA Region 2, as a companion to the Environmental Justice Demographic Screening Tool.	Similar to RAIMI and CRIA above but considers only Toxics Release Inventory (TRI) emissions, air toxics, and facility density, in screening mode. A more detailed investigation for a community's burden should be conducted at the local level.

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APPENDIX B
TOXICITY INFORMATION TO SUPPORT GROUPINGS

This appendix illustrates how toxicity data can be organized to support screening and grouping for cumulative risk assessments. Information presented here can be used in conjunction with the toxicity considerations presented in Chapter 4 and more detailed chemical-specific information when available (e.g., resources listed in Appendix A).

B.1. EXAMPLE TOXICITY MATRICES FOR SELECTED CHEMICALS

The primary toxicological effects for a set of example chemicals often encountered at a contaminated site are summarized in this appendix to illustrate how this information can be used to support grouping for an evaluation of joint toxicity and potential interactions. These chemicals were selected for study to support a site-specific integrated risk evaluation (at the U.S. Department of Energy's Hanford site). This primary toxicity information can be used to help group the chemicals by common target organ or system, by common mode of action, or by potential for interaction considering common metabolites or metabolic pathways. Primary effects for oral exposures are provided in Table B-1, and those for inhalation exposures are summarized in Table B-2. The toxicity values presented in Tables B-1 and B-2 are from U.S. EPA's IRIS database, current to November 2005. The reference doses and lowest secondary toxicological effect levels for these study chemicals are compared in Table B-3.

To simplify the presentation of information, the tables are presented together after the references for this appendix. A glossary of toxicity terms to support the grouping of chemicals by effects is presented following these tables.

B.2. SUPPORTING INFORMATION ON TOXICOLOGICAL CONCEPTS

Information used to derive the primary toxicity values – oral reference doses (RfDs) and inhalation reference concentrations (RfCs) – are provided in Section B.2.1. These primary data are also compared to the data describing effects that are considered secondary (occurring at higher doses than the primary or critical effect) in Section B.2.2.

B.2.1. Derivation of Primary Toxicity Factors. As described in EPA's document *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002e), the critical effect used in dose-response assessments is currently associated with the lowest no-observed-adverse-effect level (NOAEL), and various uncertainty factors are applied to the dose at this critical-effect level to derive the RfD or RfC. An experimental exposure level is selected from the critical-effect study that represents the highest level tested in which no adverse effect was demonstrated. This NOAEL is the key data point obtained from the study of the dose-response relationship and has traditionally served as the primary basis for evaluating potential human health risks. This approach is based on the assumption that if the critical toxic effect is prevented, then all toxic effects are prevented. A chemical can elicit more than one toxic effect , even in one test animal, or in tests of the same or different duration (acute, subchronic, and chronic exposure studies). In general, NOAELs for these effects will differ. In addition, this approach assumes that the sequence of various health effects with increasing exposure for a particular chemical is maintained across species (U.S. EPA, 2002e).

A more recent approach used to derive RfDs and RfCs is the benchmark dose (BMD) method. Use of the NOAEL in determining RfDs and RfCs has long been recognized as having limitations in that it (1) is limited to one of the doses in the study and is dependent on study design; (2) does not account for variability in the estimate of the dose-response; (3) does not account for the slope of the dose-response curve; and (4) cannot be applied when there is no NOAEL, except through application of an uncertainty factor (U.S. EPA, 2004g). A goal of the BMD approach is to define a starting point-of-departure for the computation of a reference value (RfD or RfC) or slope factor that is more independent of study design. Use of BMD methods involves fitting mathematical models to dose-response data and using the different results to select a BMD that is associated with a predetermined benchmark response, such as a 10% increase in the incidence of a particular lesion or a 10% decrease in body weight gain, which would be termed the BMD_{10} (U.S. EPA, 2004g). Note that for the study chemicals, the primary RfD for beryllium and the primary RfC for chromium VI (particulates) are both based on this newer BMD approach, as opposed to the standard NOAEL/LOAEL approach used to derive toxicity data for the other chemicals.

B.2.2. Comparison of Primary and Lowest Secondary Effects. The primary and lowest secondary effects and respective concentrations (i.e., RfDs and LOAELs/NOAELs) are given for each chemical for the oral pathway in Table B-3. The secondary effects data were selected as the lowest doses from the entire set of studies discussed in the sections on subchronic and chronic levels of significant exposure in the toxicological profiles prepared by the Agency for Toxic Substances and Disease Registry (ATSDR). Human and animal studies were evaluated separately.

As shown in this table, the lowest doses yielding secondary effects are higher than the respective RfDs for all the study chemicals. This is to be expected because RfDs are set to be protective of the lowest adverse effects, or critical effects. For all but three chemicals, the RfDs are lower than both the lowest NOAEL and LOAEL values for secondary effects from human and animal studies.

The three chemicals where RfDs could overlap NOAELs are trivalent chromium, nickel, and zinc. For trivalent chromium, nickel, and zinc, some of the lowest NOAEL values for secondary effects are below the RfD, but none of the LOAEL values for secondary effects are below the RfD. The RfD for trivalent chromium is 1.5 mg/kg-day, while the lowest animal NOAEL is a lower value of 0.46 mg/kg-day. However, the lowest animal LOAEL (5 mg/kg-day) is above the RfD. The RfD for nickel is 0.02 mg/kg-day and the lowest human NOAEL is also 0.02 mg/kg-day. No human LOAEL was reported for nickel, but the lowest animal NOAEL (0.97 mg/kg-day) is above the RfD. The RfD for zinc is 0.3 mg/kg-day, while the lowest human NOAEL is 0.06 mg/kg-day, a lower value. However, the lowest human (0.71 mg/kg-day) and animal LOAELs (0.5 mg/kg-day) are both higher than the RfD. These overlaps can be viewed as indications of the quantitiative uncertainties when using LOAELs and NOAELs.

All secondary adverse effects identified in the collection of human and animal studies reported in the ATSDR toxicological profiles for the 15 study chemicals occur at concentrations above the RfDs (all LOAELs were above the RfDs). Thus, although some actual LOAELs for secondary effects may be lower than the LOAEL for the primary effect (as discussed in Section B.2.3), the series of modifying and other

uncertainty factors applied during the RfD derivation process ensured that the RfD based on a critical effect is at least below other available LOAELs. The levels resulting in secondary effects would not typically be seen on contaminated sites, as the lowest LOAELs for secondary effects are generally several orders of magnitude higher than the RfDs. This fact is a testament to the necessity for uncertainty and other modifying factors during RfD development, given the findings noted in Section B.2. Because hazard indices estimated for contaminated sites are often less than 10, these effects would not generally be expected to occur, except in cases of high concentrations (e.g., following a major release, for which acute or short-term exposure levels would be relevant rather than chronic values), multiple routes of exposure, or where interactions occur. Thus, although effect-specific RfDs can be derived for data-rich chemicals, which would yield useful information for a cumulative risk assessment involving chemical mixtures, such an approach might not be needed. Obviously, obtaining secondary effects data for less-studied compounds would be more difficult but would give a fuller picture of the array of toxic effects exerted by each chemical. Another example of what a secondary effect analysis might find is discussed below.

B.2.3. Secondary Effects Findings: Case Study Chemicals. Although the discussion above notes that the RfDs based on primary effects appear protective of all effects for the example chemicals studied, it should be noted that the RfD or RfC is protective partly because of the use of uncertainty and/or modifying factors. Except for a few cases where no or minimal UFs are used (e.g., when chronic human toxicity data are available), part of the magnitude of UFs is to account for equitoxic dose extrapolation or scaling, and part is to be protective in the face of quantitative

uncertainty. Thus, uncertainty and modifying factors serve multiple purposes. Some secondary effects might occur at concentrations lower than the primary NOAEL or LOAEL, but because of study difficulties might have not been selected as the critical study. Consequently, one purpose of the UFs not often recognized is to provide some assurance that the RfD or RfC is protective of secondary effects.

The secondary effects summary for the study chemicals discussed below is abstracted from the ATSDR toxicological profiles and includes some examples of LOAELs for secondary effects that are lower than the primary effect LOAEL. These are the types of secondary effects that should be prioritized in a cumulative health assessment, as they would be the first to be manifested upon cumulative source or cumulative pathway exposure in addition to the primary effects. This is not a comprehensive review of all LOAELs for the study chemicals where a LOAEL is below the primary effect LOAEL, but rather a cross-section of considerations. Highlights are as follows:

- A human oral arsenic study found nervous system effects including fatigue, headaches, dizziness, insomnia, and numbness at a secondary effect LOAEL of 5×10^{-3} mg/kg-day (below the primary effect LOAEL of 1.4×10^{-2} mg/kg-day). Dermal effects of oral exposure have been documented at LOAELs below the LOAEL from the key study for the same dermal primary effect in at least three studies. Two recent studies found cardiovascular effects at a LOAEL below the dermal-based primary effect LOAEL; increased cerebrovascular disease and cerebral infarction were indicated at a LOAEL of 2×10^{-3} mg/kg-day in a 1997 study. Palpitations, chest discomfort, and cyanosis of the extremities were indicated in a 1994 study that also documented dermal effects at 5×10^{-3} mg/kg-day. Increased serum bilirubin has also been observed at a lower LOAEL than the primary effect; however, the biological significance of this endpoint alone may be questionable.

- A human inhalation study of beryllium found increased T-cell activity and chronic beryllium disease at a reported LOAEL of 5.2×10^{-4} mg/m^3 (below the primary effect LOAEL of 5.5×10^{-4} mg/m^3). Although this is

mathematically slightly lower than the study selected as the critical study in the IRIS file derivation of the RfC, the difference is not significant, as the primary effect basis for the RfC was also a human (more recent 1996) occupational study of chronic beryllium disease.

- Mercury has been reported in at least six developmental studies and seven neurological studies to result in adverse effects below the primary effect-based LOAEL of 0.633 mg/kg-day. Four studies found impacts to the kidneys at LOAELs below the primary effect-based LOAEL as well.

- For nickel, 15 studies found effects below the primary effect-based LOAEL of 50 mg/kg-day. A handful of the studies also found effects below the NOAEL of 5 mg/kg-day. Specifically, 1993, 1999, and 2000 studies (captured in the 2003 update to the ATSDR toxicological profile) indicate reproductive impacts in animals below the primary NOAEL.

- For trichloroethylene, only one study had a LOAEL below the basis for the primary effect underlying NCEA's recommended provisional value. Increased fetal heart abnormalities were noted in offspring below the LOAEL upon which the primary effect (cellular disruption) was based. U.S. EPA (2001c) evaluated this study in choosing its primary effect basis.

- Uranium studies found secondary effects at LOAELs below that which the oral RfD was based. Specifically, endocrine effects and cellular hepatic and kidney changes were observed in one study. Other minor renal effects were also noted at lower LOAELs than that used to develop the oral RfD.

Cancer data are also given in the ATSDR toxicological profiles. For example, human lung cancer and skin cancer due to arsenic exposure were also reported at LOAELs below the noncancer primary effect LOAEL; however, cancer risks are typically evaluated separately from the noncancer hazards so this would be accounted for in a cancer risk assessment.

Thus, the full body of available literature and resulting toxicity factors, NOAELs and LOAELs need to be considered and evaluated when performing a cumulative risk assessment to ensure that the risk assessment takes into account all possible significant effects and their respective effect levels. While the primary RfDs and RfCs

are considered protective and are often based on the effect seen at the lowest chemical concentration or dose, the secondary effects discussed above should be prioritized and considered in a cumulative health assessment, as they would be the first to be manifested upon cumulative source or cumulative pathway exposure in addition to the primary effects.

B.3. GLOSSARY OF TOXICOLOGICAL EFFECTS

Abdominal pain --- See Pain. Indicates effect is seen in the abdominal region.

Abnormality --- Unusual function or irregularity.

Abnormal electromyographic findings --- See Abnormality. In this effect, measurements indicating that the electrical voltage generated by body muscles is irregular.

Abnormal nerve conduction --- See Abnormality. Indicates the effect is manifested in nerve conduction.

Abortion --- The premature expulsion from the uterus of the products of conception of the embryo or of a nonviable fetus. Natural abortions are typically called miscarriages.

Aborted or stillborn fetuses --- See Abortion, Stillbirth.

Absorption alterations --- See Alterations. Indicates effect is seen in gastrointestinal tract absorption.

Acinar cell necrosis and metaplasia in pancreas --- See Necrosis and Metaplasia. Indicates effects are seen in the acinar cells of the pancreas.

Adenocarcinoma --- A form of cancer that involves cells from the lining of the walls of many different organs of the body.

Adenoma --- A benign epithelial tumor in which the cells form recognizable glandular structures or in which the cells are clearly derived from glandular epithelium.

Adhesions --- Fibrous bands or structures by which parts abnormally adhere.

Adnexal changes --- Alterations in appendages. For example, in gynecology the adnexa are the appendages of the uterus, namely the ovaries, Fallopian tubes and ligaments that hold the uterus in place.

Albuminuria --- The presence of protein in the urine, principally albumin, generally indicating disease.

Alkaline phosphatase --- An enzyme that catalyses the cleavage of inorganic phosphate non-specifically from a wide variety of phosphate esters and having a high (greater than 8) pH optimum.

Alopecia --- Baldness, absence of the hair from skin areas where it normally is present.

ALT activity changes --- Changes in a liver enzyme that plays a role in protein metabolism; see also AST. Elevated serum levels of ALT are a sign of liver damage from disease or drugs. Synonym: serum glutamic pyruvic transaminase.

Alterations --- Changes, such as increase or decrease.

Altered sperm chromatin structure --- See Alterations. Indicates effect seen in the chromatin structure of sperm.

Alveolar proteinosis --- A very rare disease in which a phospholipid is widely distributed in cells and accumulates in the alveolar spaces in the lung. In some cases the underlying cause is unknown. In others it may relate to an infection or an immune system dysfunction. The net effect is a progressive interference in the ability of the lung (alveoli) to exchange oxygen and carbon dioxide. Symptoms include cough, weight loss, fatigue, shortness of breath and nail abnormalities (clubbing).

Anemia --- Too few red blood cells in the bloodstream, resulting in insufficient oxygen supply to tissues and organs.

Anisokaryosis --- Cells or cell nuclei that vary considerably in size.

Anorexia --- The uncontrolled lack or loss of the appetite for food.

Arterial insufficiency --- Failure of arteries to function adequately, resulting in insufficient oxygen supply to cells, tissues, or organs.

Arterial [oxygen] tension --- The pressure of the blood within an artery, the arterial pressure. Also called the intra-arterial pressure.

Arterial thickening --- Increase in the thickness of the arterial walls, resulting in impaired function and restricted flow.

Arterial thickening in pancreas --- See Arterial thickening. Indicates effect is seen in the pancreas.

Arterial thickening in stomach and intestines --- See Arterial thickening. Indicates effect is seen in the stomach and intestines.

Ascites --- An effusion and accumulation of serous fluid in the abdominal cavity. Synonyms: abdominal dropsy, peritoneal dropsy, hydroperitonia, hydrops abdominis.

AST activity changes --- Changes in a liver enzyme that plays a role in protein metabolism; see also ALT. Elevated serum levels of AST are a sign of liver damage from disease or drugs. Synonym: serum glutamic oxaloacetic transaminase.

Astroglial hypertrophy --- See Astrogliosis.

Astrogliosis --- Hypertrophy of the astroglia, usually in response to injury. Astroglia (astrocytes) are the largest and most numerous neuroglial cells in the brain and spinal cord. They regulate the extracellular ionic and chemical environment, and "reactive astrocytes" (along with microglia) respond to injury.

Ataxia --- Failure of muscular coordination, irregularity of muscular action.

Atelectasis --- A term used to describe partial or complete collapse of the lung, usually due to an obstruction of a bronchus (with mucus plug, infection or cancer). Symptoms of atelectasis include low-grade fever, dry cough, chest pains and mild shortness of breath.

Atrophy --- A wasting away, a diminution in the size of a cell, tissue, organ or part.

Autoimmune glomerulonephritis --- A condition in which an individual's immune system starts reacting against his or her own tissues, causing diseases such as glomerulonephritis (inflammation of the cluster of blood vessels at the beginning of the kidney tubule where unconcentrated urine is formed by filtration of the blood).

Autonomic dysfunction --- See Dysfunction. Indicates effect is seen in the autonomic nervous system (Neurons that are not under conscious control, comprising two antagonistic components, the sympathetic and parasympathetic nervous systems. The autonomic nervous system regulates key functions including the activity of the cardiac (heart) muscle, smooth muscles (e.g., of the gut), and glands. The autonomic nervous system has two divisions: 1. The sympathetic nervous system that accelerates the heart rate, constricts blood vessels, and raises blood pressure. 2. The parasympathetic nervous system slows the heart rate, increases intestinal and gland activity, and relaxes sphincter muscles.

Azotemia --- A higher than normal blood level of urea or other nitrogen containing compounds in the blood. The hallmark test is the serum BUN (blood urea nitrogen) level. Usually caused by the inability of the kidney to excrete these compounds.

Basal cell carcinoma --- See Carcinoma. Indicates effects is seen in the relatively undifferentiated cells in an epithelial sheet that give rise to more specialized cells act as stem cells.

Behavioral changes --- See Alterations. Indicates effect is seen on normal or usual behavior.

Bile duct enlargement/proliferation --- See Enlargement, Proliferation. Indicates effect is seen in bile ducts.

Blackfoot disease --- Syndrome characterized by a progressive loss of circulation in the hands and feet, leading ultimately to necrosis and gangrene.

Blastogenesis --- Multiplication or increase by gemmation or budding.

Blastogenic activity --- See Blastogenesis.

Bleeding in the gut --- See Hemorrhage. Indicates effect is seen in the gut.

Blood phosphate --- A salt of phosphoric acid present in blood or blood serum, the clear liquid that separates from blood on clotting.

Body weight alterations --- See Alterations. Indicates effect is manifested as a change in body weight. See also Weight gain, Weight loss.

Body weight gain --- See Weight gain. Indicates effect is for whole body weight.

Body weight loss --- See Weight loss. Indicates effect is for whole body weight.

Bone accretion --- The growing together of bones.

Bone marrow retention alterations --- See Retention alterations. Indicates effect is manifested in the bone marrow.

Brain cell degeneration --- See Degeneration. Indicates effect is manifested in brain cells.

Brain, reduced number of myelinated fibers --- Fewer neural connections within the brain.

Bronchiectasis --- Persistent and progressive dilation of bronchi or bronchioles as a consequence of inflammatory disease (lung infections), obstruction (tumor) or congenital abnormality (for example cystic fibrosis). Symptoms include fetid breath and paroxysmal (spastic) coughing, with the expectoration of mucopurulent matter. It may affect the bronchioles uniformly (cylindric bronchiectasis) or occur in irregular pockets (sacculated bronchiectasis) or the dilated bronchi may have terminal bulbous enlargements (fusiform bronchiectasis).

Bronchitis --- Inflammation of one or more bronchi, usually secondary to infection.

Bronchopneumonia/bronchiopneumonia --- Inflammation of the lungs that usually begins in the terminal bronchioles. These become clogged with a mucopurulent exudate forming consolidated patches in adjacent lobules. The disease is frequently secondary in character, following infections of the upper respiratory tract, specific infectious fevers and debilitating diseases. In infants and debilitated persons of any age it may occur as a primary affection. Synonyms: bronchial pneumonia, bronchoalveolitis, bronchopneumonitis, lobular pneumonia.

Carcinoma --- A malignant new growth that arises from epithelium, found in skin or, more commonly, the lining of body organs, for example: breast, prostate, lung, stomach or bowel. Carcinomas tend to infiltrate into adjacent tissue and spread (metastasize) to distant organs, for example: to bone, liver, lung or the brain.

Cardiac inotropy --- See Inotropy. Indicates effect is seen in the cardiac muscles.

Casts (in urine) --- White blood cell casts indicate pyelonephritis, but they are not always present in the urine.

Cell-mediated cytotoxicity --- See Cytotoxicity. Indicates cells convey effect.

Cell-mediated immune response --- Immune response that involves effector T lymphocytes and not the production of humoral antibody. Responsible for delayed hypersensitivity and in defense against viral infection and intracellular protozoan parasites.

Cellular degeneration/changes --- See Degeneration. Indicates effect is seen within cells.

Central lobe necrosis --- See Necrosis. Indicates effect is seen in the central lobe of the liver.

Centrilobular necrosis --- See Central lobe necrosis.

Cerebral infarction --- Infarction of brain tissue.

Cerebrovascular disease --- A general term which encompasses a variety of diseases which affect (via the occlusive effects of atherosclerosis) the arteries which supply the brain.

Chronic conjunctivitis --- See Conjunctivitis.

Cirrhosis --- Liver disease characterized pathologically by loss of the normal microscopic lobular architecture, with fibrosis and nodular regeneration. The term is sometimes used to refer to chronic interstitial inflammation of any organ.

Cloudy swelling in kidneys --- See Inflammation. Indicates effect is seen in kidneys.

Confusion --- Disturbed orientation in regard to time, place or person, sometimes accompanied by disordered consciousness.

Congenital malformations --- Abnormal formation of a structure evident at birth

Conjunctivitis --- Inflammation of the conjunctiva, generally consisting of conjunctival hyperemia associated with a discharge.

Contractility --- Capacity for becoming short in response to a suitable stimulus.

Cough --- A rapid expulsion of air from the lungs typically in order to clear the lung airways of fluids, mucus, or material.

Cramps --- See Pain. Indicates effect is seen in abdomen.

Cyanosis --- A bluish discoloration, applied especially to such discoloration of skin and mucous membranes due to excessive concentration of reduced hemoglobin in the blood.

Cysts --- Any closed cavity or sac that is lined by epithelium often contains liquid or semi-solid material.

Cytomegaly --- A condition or disease characterized by abnormally enlarged cells.

Cytotoxicity --- The quality of being poisonous, or toxic, to individual cells.

Damage --- See Injury.

Death --- See Survival.

Decline in conditioned responses --- Reduced frequency of learned behaviors in response to triggering stimulus.

Decrease in Hb and H values --- Lowered hemoglobin content, resulting in reduced oxygen carrying capacity and possible anoxia. Hemoglobin is the Four subunit globular oxygen carrying protein of vertebrates and some invertebrates. There are two alpha and two beta chains (very similar to myoglobin) in adult humans, the heme moiety (an iron-containing substituted porphyrin) is firmly held in a nonpolar crevice in each peptide chain.

Decreased alkaline phosphatase --- See alkaline phosphatase.

Decreased arterial tension --- See arterial tension. Reduction in the pressure of blood within an artery.

Decreased avoidance response --- Reduction in learned ability to respond to a cue that is instrumental in avoiding a noxious experience.

Decreased blood or serum phosphate levels --- See blood phosphate and serum phosphate.

Decreased cardiac contractility --- See contractility. Indicates effect is seen in the cardiac muscles.

Decreased caudal ossification --- See Ossification. Indicates effect is seen at a position more toward the cauda or tail of an organism.

Decreased corpuscular volume --- See Anemia. Indicates reduced volume of red blood cells.

Decreased DNA in brain areas --- Reduction in genetic material in the brain.

Decreased fetal body weight --- See Weight Loss. Indicates decrease is in the fetus.

Decreased immunoglobulins --- Reduction in the specific protein substances that are produced by plasma cells to aid in fighting infection. Some immunoglobulins (gamma globulin) take part in various immune responses of the body to bacteria or foreign substances (allergens, tumor or transplanted tissue). Examples include IgG, IgM, IgA, IgD and IgE.

Decreased macrophage activity --- Reduction in the function of macrophages, which are relatively long lived phagocytic cell of mammalian tissues, derived from blood monocyte. Macrophages from different sites have distinctly different properties. Macrophages play an important role in killing of some bacteria, protozoa and tumor cells, release substances that stimulate other cells of the immune system and are involved in antigen presentation.

Decreased pulmonary bactericidal activity --- Reduction in the body's defense mechanisms to kill bacteria in the lungs.

Decreased response rate for learned behaviors --- Increased time to respond to triggering stimuli. See also Decline in Conditioned Responses.

Decreased tactile-kinesthetic function --- Reduction of the tactile the sense of touch or pressure by which muscular motion, weight, position, are perceived.

Decreased T-cell activity --- See T-cell.

Decreased sperm count --- Decrease in the number of sperm in the ejaculate (when given as the number of sperm per milliliter it is more accurately known as the sperm concentration or sperm density).

Decreased survival --- See Survival.

Decreased vasoreactivity --- Reduction in the blood vessels' ability to change caliber in response to stimulus, thus affecting blood flow.

Degeneration --- Reduced size or function of a cell, tissue, organ, or part.

Dehydration --- Excessive loss of body water.

Delayed ossification --- Indicates a delay in the formation of bone or of a bony substance, the conversion of fibrous tissue or of cartilage into bone or a bony substance. See also Reduced Ossification.

Demyelination --- See Myelin degeneration.

Depigmentation --- See Pigmentation changes. The removal or loss of pigment, especially melanin.

Depression --- A lowering or decrease of functional activity. Also a mental state of depressed mood characterized by feelings of sadness, despair and discouragement. Depression ranges from normal feelings of the blues through dysthymia to major depression.

Dermal effects --- Effects on the skin.

Dermatitis --- Inflammation of the skin.

Desquamation of tubular cells --- The shedding or exfoliation of epithelial elements of the renal tubules.

Diabetes mellitus --- Relative or absolute lack of insulin leading to uncontrolled carbohydrate metabolism. In juvenile onset diabetes (that may be an autoimmune response to pancreatic cells) the insulin deficiency tends to be almost total, whereas in adult onset diabetes there seems to be no immunological component but an association with obesity.

Diarrhea --- A morbidly frequent and profuse discharge of loose or fluid evacuations from the intestines, without tenesmus; a purging or looseness of the bowels; a flux.

Diffuse erythematous and scaly rash --- Redness and scaling of the skin produced by congestion of the capillaries, which may result from a variety of causes.

Diffuse palmar or plantar hyperkeratosis --- See Hyperkeratosis. Indicates effect is seen on palms of hands and soles of feet, and is widespread in nature.

Diffuse pigmentation --- See Pigmentation. Indicates pigmentation is widespread.

Dilation --- Expanded in internal diameter.

Disorientation --- See Confusion.

Distribution alterations --- Changes in distribution.

Diuresis --- Increased excretion of urine. Can be due to metabolic conditions such as diabetes, where the increased glucose level in the blood causes water to be lost in the urine. Can also be produced specifically by diuretic drugs that increase sodium and water loss from the kidney.

DOPAC (Dopachrome oxidoreductase) --- Decarboxylates and converts dopachrome to 5,6-dihydroxyindole.

Dysfunction --- Failure to function normally.

Dyspepsia --- Difficult or painful digestion, indigestion.

Edema --- The presence of abnormally large amounts of fluid in the intercellular tissue spaces of the body, usually applied to demonstrable accumulation of excessive fluid in the subcutaneous tissues. Edema may be localized, due to venous or lymphatic obstruction or to increased vascular permeability or it may be systemic due to heart failure or renal disease. Collections of edemous fluid are designated according to the site, for example ascites (peritoneal cavity), hydrothorax (pleural cavity) and hydropericardium (pericardial sac). Massive generalized edema is called anasarca.

Embryolethality --- See Abortion, Stillbirth.

Emaciation --- Excessive leanness; a wasted condition of the body.

Emesis --- Vomiting, an act of vomiting. Also used as a word termination, as in hematemesis.

Emphysema --- A pathological accumulation of air in tissues or organs, applied especially to such a condition of the lungs.

Encephaloceles --- Hernia of the brain; infarction of brain tissue.

Enhanced inflammatory response --- Increased sensitivity to tissue injury causing an inflammatory response, which is a part of innate immunity. Inflammation occurs when tissues are injured by viruses, bacteria, trauma, chemicals, heat, cold or any other harmful stimulus. Chemicals including bradykinin, histamine, serotonin and others are released by specialized cells. These chemicals attract tissue macrophages and white blood cells to localize in an area to engulf (phagocytize) and destroy foreign substances. A byproduct of this activity is the formation of pus, which is a combination of white blood cells, bacteria, and foreign debris.

Enlarged nuclei --- Increase in size of the cellular nucleus.

Enlarged nuclei of tubular cells --- See Enlarged nuclei. Indicates cells affected are kidney tubular cells.

Enlargement --- Increased size. See also Weight gain.

Enzyme activity stimulation --- See Increased enzyme activity.

Enzyme inhibition -- Arrest or restraint of a enzyme process(es).

Eosinophilia -- The formation and accumulation of an abnormally large number of eosinophils in the blood.

Epitaxis (epitasis) --- The period of violence in a fever or disease; paroxysm.

Epithelial degeneration --- See Degeneration. Indicates effect is manifested in the epithelium.

Epithelial degradation --- See Epithelial degeneration.

Eroded luminal epithelium in the stomach --- See Degeneration. Indicates effect is seen in the luminal epithelium of the stomach.

Erythroid hyperplasia of bone marrow --- See Hyperplasia. Indicates effect is seen in erythrocytes of the bone marrow.

Exencephaly --- See Terata. Condition in which the brain is located outside of the skull. This condition is usually found in embryos as an early stage of anencephaly. As an exencephalic pregnancy progresses, the neural tissue gradually degenerates. It is unusual to find an infant carried to term with this condition because the defect is incompatible with survival.

Excretion reduction --- A decline in production of waste products. See also Abnormal Retention. May include reduced urinary output.

Eye defects in fetus --- See Terata. Indicates malformation of the fetal eye.

Fatigue --- Weakness.

Fatty changes --- See Fatty infiltration.

Fatty infiltration --- Accumulation of fatty acids as triglycerides in the liver. Focal fatty infiltration may mimic neoplastic or other low-density parenchymal lesions, including abscesses and hemangiomas. Fatty liver has also been associated with diabetes, obesity, use of corticosteroids and other drugs (including chemotherapy), Cushing's disease, total parenteral nutrition, starvation, hyperlipidemia, pregnancy, cystic fibrosis, Reye's syndrome, malignancy, jejunoileal bypass, and other causes.

Fertility --- The capacity to conceive or induce conception and thus generate offspring.

Fetotoxicity --- Toxicity manifested in the fetus.

Fibrosis --- The formation of fibrous tissue, fibroid or fibrous degeneration.

Focal necrosis --- See Necrosis. Indicates effect is seen in localized area.

Folliculitis --- Inflammation of a follicle or follicles, used ordinarily in reference to hair follicles, but sometimes in relation to follicles of other kinds.

Functional denervation --- Reduced capacity of existing neurons resulting in effective disfunction at the neural termination.

Functional impairment --- Reduction of normal function in a cell, organ, tissue, or part.

Gangrene --- Death of tissue, usually in considerable mass and generally associated with loss of vascular (nutritive) supply and followed by bacterial invasion and putrefaction.

Gasping --- The act of opening the mouth convulsively to catch the breath; a labored respiration; a painful catching of the breath.

Gastrointestinal hemorrhage --- See Hemorrhage. Indicates effect is seen in the gastrointestinal tract.

Gastrointestinal irritation --- See Irritation. Indicates effect is seen in the gastrointestinal tract.

Genitourinary defects --- See Terata. Indicates malformation occurring in the (urogenital) genital and urinary organs.

Glucosuria -- A condition in which glucose is discharged in the urine; diabetes mellitus.

Glycogen level changes --- Alterations in levels of the branched polymer of D glucose, which serves as the major short-term storage polymer of animal cells and is particularly abundant in the liver and to a lesser extent in muscle.

Granule cell loss --- Reduction in number of granule cells, a type of neuron, in the cerebellum.

Granuloma --- Chronic inflammatory lesion characterized by large numbers of cells of various types (macrophages, lymphocytes, fibroblasts, giant cells), some degrading and some repairing the tissues.

Granulomata --- See Granuloma.

Gross gastrointestinal lesions --- See Lesions. Indicates widespread effect is seen in the gastrointestinal tract.

Gross physical abnormalities --- See Terata. Indicates fetal malformations are significant and relate to the basic components of the body. See also Skeletal Malformations, Increases in Skeletal Variations.

Headache --- See Pain. Indicates effect is seen in the head or sinuses.

Heart abnormalities in fetus --- See Terata. Indicates malformations affecting the heart.

Heart disease --- Common condition where vessels (arteries) that carry blood to the heart muscle become narrowed with fatty deposits. The heart then cannot get the oxygen and other nutrients it needs. A complete blockage of one of these vessels may result in a heart attack.

Hematemesis --- The vomiting of blood.

Hemolysis --- Disruption of the integrity of the red cell membrane causing release of hemoglobin.

Hemoperitoneum --- Intraabdominal bleeding, accompanied by abdominal pain. The liver or spleen may increase in size. If the bleeding is severe enough, the blood pressure and hematocrit may fall.

Hemorrhage --- Bleeding. The escape of blood from the vessels. Small hemorrhages are classified according to size as petechiae (very small), purpura (up to 1 cm) and ecchymoses (larger). The massive accumulation of blood within a tissue is called a hematoma.

Hemosiderin deposits --- Deposits of a mammalian iron storage protein (related to ferritin but less abundant).

Hemosiderin deposits in hepatic macrophages --- See Hemosiderin deposits. Indicates effect is seen in liver macrophages, which are relatively long-lived phagocytic cells of mammalian tissues, derived from blood monocytes.

Hemosiderin deposits in liver --- See Hemosiderin deposits. Indicates effect is seen in liver.

Hemosiderin deposits in kidney --- See Hemosiderin deposits. Indicates effect is seen in kidney.

Hepatoma --- Carcinoma derived from liver cells. Also known as hepatocarcinoma or hepatocellular carcinoma.

Hepatomegaly --- Enlargement of the liver.

Hepatotoxicity --- Toxicity manifested in the liver.

Histopathological changes --- Microscopic changes in diseased tissues.

Histopathological changes in heart tissue --- See Histopathological changes. Indicates effect is manifested in heart tissue.

Histopathological changes in lungs --- See Histopathological changes. Indicates effect is manifested in lung tissue.

Humoral immune response --- Immune responses mediated by antibodies.

Hypalgesia --- Decreased pain response.

Hyperemia --- An excess amount of blood in an organ. Active hyperemia is increased blood supply to an organ, usually for physiologic reasons (exercise). Passive hyperemia is engorgement of an organ with venous blood, usually the result of inadequate circulation (heart failure).

Hyperkeratosis --- Hypertrophy of the corneous layer of the skin, or any of various conditions marked by hyperkeratosis.

Hyperkeratosis of foot --- See Hyperkeratosis. Indicates effect is seen in the feet.

Hyperpigmentation --- Darkening of the skin. See also Pigmentation.

Hyperplasia --- The abnormal multiplication or increase in the number of normal cells in normal arrangement in a tissue.

Hypertension --- Persistently high arterial blood pressure. Hypertension may have no known cause (essential or idiopathic hypertension) or be associated with other primary diseases (secondary hypertension). This condition is considered a risk factor for the development of heart disease, peripheral vascular disease, stroke and kidney disease.

Hypertrophy --- The enlargement or overgrowth of an organ or part due to an increase in size of its constituent cells.

Hypertrophy of pancreas islet cells --- See Hypertrophy. Indicates effect is seen on the cells of the Islets of Langerhans (or islet cells) within the pancreas.

Hypoplasia --- The incomplete development or underdevelopment of an organ or tissue.

Hypopigmentation --- A condition caused by a deficiency in melanin formation or a loss of pre-existing melanin or melanocytes. It can be complete or partial and may result from trauma, inflammation, and certain infections.

Hypothermia -- A low body temperature, as that due to exposure in cold weather or a state of low temperature of the body induced as a means of decreasing metabolism of tissues and thereby the need for oxygen, as used in various surgical procedures, especially on the heart or in an excised organ being preserved for transplantation.

Impaired lymphocytic/leukocytic function --- See impairment. Indicates effect is seen in the normal function of lymphocytes and leukocytes.

Impaired peripheral vision --- Reduction in visual capacity, particularly in the periphery of the normal field of vision.

Impaired liver mitochondrial respiration - See Impairment. Indicates effect is seen in the respiration of the liver mitochondria.

Impaired renal mitochondrial respiration - See Impairment. Indicates effect is seen in the respiration of the kidney mitochondria.

Impairment --- Reduction in normal function.

Increased cerebral infarction --- Infarction (an area of tissue death due to a local lack of oxygen) of brain tissue.

Increased cerebrovascular disease --- Increase in any of a variety of diseases which affect (via the occlusive effects of atherosclerosis) the arteries which supply the brain. May lead to stroke.

Increased DOPAC concentration --- See DOPAC, increased enzyme activity, and increased enzyme levels.

Increased enzyme activity --- Metabolic increase via stimulation of enzyme systems.

Increased enzyme levels --- See Increased enzyme activity. Higher measurable circulating or tissue enzymes.

Increased glycogen --- see Glycogen level changes.

Increased heart weight --- See Organ weight gain. Indicates effect is manifested in the heart tissue.

Increased kidney weight--- See Organ weight gain. Indicates effect is manifested in the kidney tissue.

Increased leukocyte count --- An abnormal accumulation of white blood cells.

Increased liver weight --- See Organ weight gain. Indicates effect is manifested in the liver tissue.

Increased lung weight --- See Organ weight gain. Indicates effect is manifested in the lung tissue.

Increased MCH --- See MCH, increased enzyme activity, and increased enzyme levels.

Increased resorptions --- The loss of substance through physiologic or pathologic means, such as loss of dentin and cementum of a tooth or of the alveolar process of the mandible or maxilla. In a reproductive context, implies embryos are not carried to term but are instead absorbed into the uterine wall. See also Fertility, Reduced Birth Rate, and Reduced Litter Size, as increased resorptions are related to pregnancy outcome.

Increased response to sheep red blood cells --- Heightened sensitivity to immune challenge.

Increased serum enzyme levels --- See Increased enzyme levels. Indicates effect is manifested in circulating serum enzymes.

Increased SGOT --- See SGOT, increased enzyme activity, and increased enzyme levels.

Increased skeletal variations --- See Terata. See also Gross physical abnormalities.

Increased stillbirth --- See Stillbirth.

Increased urea --- See urea. Indicates a higher than normal excretion of urea in urine.

Increased vasopasticity --- Enhanced constriction of blood vessels.

Inflammation --- A localized protective response elicited by injury or destruction of tissues, which serves to destroy, dilute or wall off (sequester) both the injurious agent and the injured tissue. Histologically, it involves a complex series of events, including dilatation of arterioles, capillaries and venules, with increased permeability and blood flow, exudation of fluids, including plasma proteins and leukocytic migration into the inflammatory focus.

Infiltration --- The diffusion or accumulation in a tissue or cells of substances not normal to it or in amounts of the normal. Also, the material so accumulated. See Macrophage infiltration.

Inotropy --- Muscular contractions.

Interstitial bronchiole pneumonia --- See Bronchiopneumonia. Indicates effect is seen in the interspaces of the lung tissue.

Interstitial lung disease --- A heterogeneous group of noninfectious, nonmalignant disorders of the lower respiratory tract, affecting primarily the alveolar wall structures but also often involving the small airways and blood vessels of the lung parenchyma. "interstitial" refers to the fact that the interstitium of the alveolar walls is thickened, usually by fibrosis. This group of diseases is usually inflammatory.

Intraepidermal carcinoma--- See Carcinoma. Indicates effect is seen within the epidermis.

Intromission --- Insertion; introduction.

Initial body weight loss --- See Weight loss.

Injury --- Result of assault by an external force, organic or physiologic dysfunction, or a pathogen.

Intestinal hyperemia --- See Hyperemia. Congestion of the blood in the intestines.

Irritation of the eyes --- See Irritation. Indicates effect is seen in the eye.

Irritation --- Local inflammation of cutaneous or mucosal surfaces.

Ischemic heart disease --- Disease of the heart characterized by a low oxygen state usually due to obstruction of the arterial blood supply or inadequate blood flow leading to hypoxia in the tissue.

Karyomegaly -- The condition of a cells nucleus being abnormally enlarged (i.e., for reasons other than it being polyploid).

Keratosis --- A skin lesion that is abnormally sensitive to the effects of ultraviolet light (sunlight). Thought to be a precancerous skin lesion that is more common in the fair-skinned or elderly individual. Usually a discrete slightly raised, red or pink lesion located on a sun-exposed surface. Texture may appear as rough, gritty or scaly.

Labored breathing --- See Gasping.

Lesions --- Any pathological or traumatic discontinuity of tissue or loss of function of a part.

Lassitude --- Weakness, exhaustion.

Leukocytosis -- A term used to describe an abnormal elevation on the white blood cell count. Elevated counts can be seen in cases of inflammation and infection.

Leukoderma --- An acquired disorder that selectively destroys (or that results in the selective disappearance) of some or all melanocytes residing in the interfollicular epidermis and occasionally in the follicle as well. The mechanism(s) by which the melanocytes are lost (or by which melanocytes are made to disappear) may be multiple but are not yet identified unequivocally.

Leukopenia --- Abnormal decrease in the number of white blood cells.

Lethal Dose 50 --- The amount, or dosage, of a toxin necessary to kill 50% of the experimental subjects.

Leydig cell tumor --- The most common nongerminal tumor of the testis, derived from the leydig cells. It is rarely malignant. This tumor appears among 1-3% of testicular tumors and although they may be seen in children, the median age of appearance is 60 years. They are sometimes seen in women as ovarian tumors. Clinically, symptoms are usually related to the endocrine abnormalities induced by this tumor.

Lipid peroxidation --- Peroxidase-catalyzed oxidation of lipids using hydrogen peroxide as an electron acceptor.

Loss of circulation --- Reduced oxygen supply to cells, organs, or parts.

Loss of dexterity --- Decrease in readiness and grace in physical activity; decrease in skill and ease in using the hands.

Lung irritation --- See Irritation. Indicates effect is manifested in the lung.

Lymphoma --- Malignant tumor of lymphoblasts derived from B lymphocytes.

Lysosomal inclusions --- Accumulations of the undigested substrate within cells caused by an enzyme deficiency.

MCH (Mch4 proteaseAn) --- An enzyme. An aspartate-specific cysteine protease containing two fadd-like domains.

Macrocytic anemia --- See Anemia. Indicates the effect is caused by enlarged red blood cells.

Macrophage infiltration --- See Infiltration. Indicates effect is an accumulation of macrophages.

Melanoderma --- Abnormal blackness of skin.

Melanosis --- A disorder caused by a disturbance in melanin pigmentation; melanism.

Melena --- Bloody or dark black or tarry bowel movements.

Memory loss --- Disturbances in registering an impression, in the retention of an acquired impression or in the recall of an impression.

Mental sluggishness --- Delayed reactions or fatigue arising in consequence of mental effort.

Metabolism alterations --- See Alterations. Indicates the effect is manifested in metabolic processes; may reflect and increase or decrease in metabolism.

Metaplasia --- The change in the type of adult cells in a tissue to a form that is not formal for that tissue.

Methemoglobinemia --- The presence of methemoglobin in the blood, resulting in cyanosis. A small amount of methemoglobin is present in the blood normally, but injury or toxic agents convert a larger proportion of hemoglobin into methemoglobin, which does not function reversibly as an oxygen carrier.

Microgranuloma --- See Granuloma. Indicates the effect is small, little.

Mineralization --- Production of bone minerals from collagen, important in the progressive growth and development of normally calcifying bone, cartilage, tendon, dentin, and cementum among vertebrate tissues. Collagen represents the principal organic component in such tissues and it strictly mediates the nucleation, growth, and development of the mineral, a calcium phosphate salt (apatite). The interaction between collagen and mineral leads to a composite tissue having improved strength and biomechanical properties different from those of either component separately considered. Conversely, changes in collagen content, assembly, or aggregation could have profound effects on mineralization and subsequently on the nature of tissue integrity and mechanical behavior.

Miscarriage --- See Abortion.

Mitochondrial Respiration Impairment --- See Impairment. Indicates reduction in the energy produced in the mitochondria, which are specialized membrane structures within a cell that provide energy for a cell by the addition of substances acted upon by enzymes

Mortality --- See Survival.

Motility --- Ability of the spermatozoa to move by flagellate swimming.

Muscular hypertrophy --- see Hypertrophy.

Myelin degeneration --- See Degeneration. Indicates the effect is seen in the material making up the myelin sheath of nerve axons.

Narcosis --- State of unconsciousness.

Nausea --- An unpleasant sensation, vaguely referred to the epigastrium and abdomen and often culminating in vomiting. See Also Dyspepsia, Emesis, Vomiting.

Necrosis --- Death of a tissue.

Nephrosis --- A type of nephritis that is characterized by low serum albumin, large amount of protein in the urine and swelling (edema). Swelling, weight gain, high blood pressure and anorexia are key features. Nephrotic syndrome can be seen with a number of illness that cause damage to the kidney glomerulus. Examples include diabetes, hereditary disorders, lupus, multiple myeloma, amyloidosis, glomerulonephritis, minimal change disease and membranous glomerulonephritis.

Nephrotoxicity --- Toxicity to the kidney.

Nerve conduction --- Neural transport of an electronic impulse.

Neuropathy --- A general term denoting functional disturbances and/or pathological changes in the peripheral nervous system. If the involvement is in one nerve it is called mononeuropathy, in several nerves, mononeuropathy multiplex, if diffuse and bilateral, polyneuropathy. The etiology may be known for example arsenical neuropathy, diabetic neuropathy, ischemic neuropathy, traumatic neuropathy) or unknown. Encephalopathy and myelopathy are corresponding terms relating to involvement of the brain and spinal cord, respectively. The term is also used to designate noninflammatory lesions in the peripheral nervous system, in contrast to inflammatory lesions (neuritis).

Neonatal survival --- See Perinatal mortality.

Nonspecific brain injury --- See Injury. Indicates effect is seen in the brain, but specific etiology or precise effect is unknown.

Nonspecific hepatotoxicity --- See Hepatotoxicity.

Not specified --- Not otherwise specified. No additional information is immediately available.

Numbness --- Lacking sensation.

Oliguria --- Secretion of a diminished amount of urine in relation to the fluid intake.

Ossification -- The formation of bone or of a bony substance, the conversion of fibrous tissue or of cartilage into bone or a bony substance.

Organ Weight Gain --- Increase in the mass of an organ. May indicate injury to the organ or increase in organ function in response to a stimulus.

Ossification --- the formation of bone or of a bony substance, the conversion of fibrous tissue or of cartilage into bone or a bony substance. See Delayed ossification; Reduced ossification.

Osteomalacia -- A condition marked by softening of the bones (due to impaired mineralization, with excess accumulation of osteoid), with pain, tenderness, muscular weakness, anorexia and loss of weight, resulting from deficiency of vitamin D and calcium.

Osteoporosis --- A reduction in the amount of bone mass, leading to fractures after minimal trauma.

Pain --- Sensation of discomfort, distress, or agony.

Pale skin --- Skin lacking freshness or ruddiness; a sickly whiteness; lack of color or luster; wanness.

Palmar and plantar keratosis --- See Keratosis. Indicates effect is seen on palms of hands and soles of feet.

Palpitations --- Irregular and violent heartbeats.

Pancreatitis --- Acute or chronic inflammation of the pancreas, which may be asymptomatic or symptomatic and which is due to autodigestion of a pancreatic tissue by its own enzymes.

Paresthesia --- Paralysis.

Perforation --- A hole made through a part or substance.

Periocular edema --- See Edema. Indicates effect is seen around the eyes.

Perinatal mortality --- Mortality occurring in the period shortly before and after birth, (in humans defined as beginning with completion of the twentieth to twenty eighth week of gestation and ending 7 to 28 days after birth); see also Stillbirth, Abortion, Mortality.

Peripheral nervous system impairment --- See Impairment. Indicates effect is seen in the nerves of the PNS, which connect the central nervous system (CNS) with sensory organs, other organs, muscles, blood vessels, and glands.

Peripheral --- Pertaining to or situated at or near the periphery, situated away from a center or central structure.

Persistent extensive hyperkeratosis --- See Hyperkeratosis. Indicates condition is widespread and difficult to treat.

Pharyngitis --- Inflammation of the pharynx.

Pheochromocytoma --- A tumor of the adrenal gland, which produces catecholamines (noradrenaline and adrenaline). Although the tumor is usually benign it produces hypertension, pounding headaches, tachycardia, palpitations, apprehension, facial flushing, nausea and vomiting.

Pigmentation --- Coloration, especially abnormally increased coloration, by melanin.

Pigmentation changes --- Increase or decrease in pigment, especially melanin.

Pigmentation in hepatic macrophages --- See Pigmentation. Indicates effect is seen in the liver macrophages, which are relatively long-lived phagocytic cells derived from blood monocytes.

Pneumonia --- Inflammation of the lungs with consolidation.

Pneumonitis --- Inflammation of the lung secondary to viral or bacterial infection.

Portal hypertension --- Any increase in the portal vein (in the liver) pressure due to anatomic or functional obstruction (for example alcoholic cirrhosis) to blood flow in the portal venous system. Indicators of portal hypertension are: esophageal varices, hemorrhoids, enlarged veins on the anterior abdominal wall (caput Medusae) and ascites.

Possible vascular complications --- See Vascular complications.

Production --- Creation of a product.

Proliferation --- Increase in numbers; the reproduction or multiplication of similar forms, especially of cells and morbid cysts.

Prostration --- Absolute exhaustion.

Proteinuria --- Too much protein in the urine. This may be a sign of kidney damage.

Pulmonary vasculitis --- See Vasculitis. Indicates effect is seen in the respiratory tract.

Rales --- Abnormal breathing sounds heard through a stethoscope.

Raynaud's disease --- Paroxysmal (i.e., occurring in spasms or seizures) bilateral cyanosis of the digits due to arterial or arteriolar contraction.

RBC functional impairment --- See Impairment. Indicates failure of the red blood cells to function, primarily resulting in poor oxygen distribution.

Reduced birth rate --- Fewer live births than expected. See also Stillbirth, Increased resorptions, Abortion, and Reduced fertility.

Reduced growth rate --- Failure to gain weight normally. See also Weight gain, Weight loss.

Reduced clavicle --- Also called the collar bone, it articulates with the shoulder on one end (at the acromion process of the scapula) and the sternum (breast bone) on the other.

Reduced fertility --- See Fertility. Failure to conceive normally.

Reduced fine motor performance --- See Impairment. Indicates effect is noted in fine motor skills.

Reduced glycogen --- Reduction in the polysaccharide occurring especially in the liver and muscle, where it is stored as a sugar-supply reserve, capable of complete conversion to glucose when needed. See also Glycogen level changes.

Reduced heart rate --- Depressed heart rate.

Reduced litter size --- See Reduced birth rate.

Reduced lung function --- See Impairment. Indicates effect is seen on pulmonary function.

Reduced nerve conduction --- See Impairment. Indicates effect is seen in nerve conduction.

Reduced ossification --- Indicates a reduction in the formation of bone or of a bony substance, the conversion of fibrous tissue or of cartilage into bone or a bony substance. See also Delayed Ossification.

Reduced short-term memory --- See Memory Loss. Indicates effect is manifested in short-term retention.

Reduced sperm motility --- See Motility. See also Fertility. Indicates effect is seen in sperm.

Reduced sperm production --- See Production. See also Fertility. Indicates effect is seen in sperm.

Reduced urinary output --- Lower volume (whether due to excretion reduction or concentration of wastes) of urine production. See also Excretion Reduction.

Respiratory tract inflammation --- See Inflammation. Indicates effect is seen in the respiratory tract.

Resorption --- The loss of substance through physiologic or pathologic means.

Respiratory tract injury --- See Injury. Indicates effect is seen in the respiratory tract.

Retention alterations --- Changes in the persistent keeping within the body of matters normally excreted; thus, decreased excretion is also increased retention. See also Excretion Reduction.

Reticulin sclerosis --- See Sclerosis. Indicates effect is seen in the reticulin, the constituent protein of reticulin fibers found in extracellular matrix.

Rhinitis --- Inflammation of the mucous membrane of the nose.

Rhinorrhea --- The free discharge of a thin nasal mucus.

Rickets --- A condition caused by deficiency of vitamin D, especially in infancy and childhood, with disturbance of normal ossification. The disease is marked by bending and distortion of the bones under muscular action, by the formation of nodular enlargements on the ends and sides of the bones, by delayed closure of the fontanelles, pain in the muscles and sweating of the head.

Scaling --- Dry patches of skin resembling fish scales. See also Dermatitis.

Scaling of skin --- See Scaling.

Sciatic and optic nerve injury --- See Injury. Indicates effect is seen in the sciatic (hip region) and optic (eye) nerves.

Sclerosis --- An induration or hardening, especially hardening of a part from inflammation and in diseases of the interstitial substance. The term is used chiefly for such a hardening of the nervous system due to hyperplasia of the connective tissue or to designate hardening of the blood vessels.

Seizures --- Attacks of cerebral origin consisting of sudden and transitory abnormal phenomena of a motor, sensory, autonomic or psychic nature resulting from transient dysfunction of the brain.

Serum phosphate --- See blood phosphate.

SGOT --- An enzyme produced by the liver. Elevated levels of SGOT in the blood indicate a liver problem.

Skeletal defects --- See Terata. Indicates skeletal malformation, may be a considered a (see also) Gross Physical Abnormality.

Skin inflammation --- See Dermatitis.

Sleep disorders --- Disturbances of usual sleep patterns or behaviors.

Spasm of digital arteries --- A sudden but transitory constriction of the arteries of the digits (e.g., one of the terminal divisions of a limb appendage, such as a finger or toe).

Squamous cell carcinoma --- See Carcinoma. Indicates effect is seen in the flat thin cells found in the outer layer of the skin.

Stillbirth --- Delivery of a dead fetus. See also Abortion.

Stomach adhesions --- See Adhesions. Indicates effect is seen in the stomach.

Survival --- Living or continuing living. Decreased survival is increased mortality, increased death rate.

Swelling of the eyes --- See Edema. Indicates effect is seen in or near the eyes.

T-cell --- A class of lymphocytes, so called because they are derived from the thymus and have been through thymic processing. Involved primarily in controlling cell-mediated immune reactions and in the control of B-cell development. The T-cells coordinate the immune system by secreting lymphokine hormones.

Terata --- Malformation in an embryo; birth defect.

Testicular degeneration or atrophy --- See Degeneration, Atrophy. Indicates effect is seen in the testicles.

Thin and dilated coronary arteries --- See Thinning, Dilation. Indicates effect is seen in coronary arteries.

Thinning --- Reduced thickness, as of vessel walls.

Thrombosis --- The formation, development or presence of a thrombus.

Tingling of hands and feet --- Detection of a feeling in extremities indicated.

Tonsilitis --- Inflammation of the tonsil.

Toxic nephrosis --- Toxicity or destruction observed in kidney cells. See also Nephrotoxicity.

Tremors --- An involuntary trembling or quivering.

Trembling --- See Tremors.

Tubular degeneration --- See Degeneration. Indicates effect is seen in kidney tubules.

Ulcer --- A local defect or excavation, of the surface of an organ or tissue, which is produced by the sloughing of inflammatory necrotic tissue.

Ulceration --- See Ulcer. The formation or development of an ulcer.

Ulcerative cecitis --- Inflammation of the cecum, a blind pouch-like commencement of the colon in the right lower quadrant of the abdomen at the end of the small intestine. The appendix is a diverticulum that extends off the cecum.

Urea --- The final nitrogenous excretion product of many organisms.

Vacuolization --- Formation into, or multiplication of, vacuoles.

Vacuolization of fasciculata cells in adrenal cortex --- See Vacuolization. Indicates effect is seen on the fasciculata cells in adrenal cortex, the outer portion of the fatty acids that inhibit inflammation in allergic responses.

Vacuolization of pancreas islet cells --- See Vacuolization. Indicates effect is seen on the cells of the Islets of Langerhans (or islet cells) within the pancreas.

Vascular complications --- Complications pertaining to blood vessels or indicative of a copious blood supply.

Vasculitis --- Inflammation of a vessel.

Vesiculation --- The state of containing vesicles, or the process by which vesicles are formed. A vesicle is a closed membrane shell, derived from membranes either by a physiological process (budding) or mechanically by sonication.

Viability --- The quality or state of being viable; specifically, the capacity of living after birth.

Vibration sensation --- Detection of a feeling of oscillation.

Vomiting --- See Emesis. See also Nausea, Dyspepsia.

Wart formation --- Formation of a benign tumor of basal cell of skin, the result of the infection of a single cell with wart virus (Papilloma virus). Virus is undetectable in basal layer, but proliferates in keratinizing cells of outer layers.

Weight gain --- Increase in body mass.

Weight loss --- Decrease in body mass.

Note: These definitions have been adapted from the following sources:

The On-line Medical Dictionary (c) Academic Medical Publishing & CancerWEB 1997-98. Available at http://www.betterhealth.vic.gov.au/bhcv2/bhcsite.nsf/pages/bhc_medicaldictionary?opendocument. Accessed July-September 2001. Distributed by CancerWEB under license from Academic Medical Publishing.

The New Lexicon: Webster's Dictionary of the English Language. 1989 edition. Lexicon Publications, Inc., New York, NY.

ATSDR (Agency for Toxic Substances and Disease Registry). 2000a. Toxicological Profile for Arsenic (Update). September.

E-Doc (Electronic Doctor) Index of Medical Terminology. (c) E-Doc 1998-99. Available at http://www.edoc.co.za/.

TABLE B-1

Primary Effects from Oral Exposures[a]

Chemical	Primary System/Organ Affected	Primary Noncancer Effect	Primary Effect LOAEL (mg/kg-day)	Oral RfD (mg/kg-day)	Oral RfD Combined Uncertainty Factor/Modifying Factor
Arsenic (inorganic) (As)	Skin, cardiovascular system	Hyperpigmentation, keratosis, possible vascular complications	0.014	0.0003	3
Beryllium (Be)	Gastrointestinal system	Small intestinal lesions	Not established (benchmark dose is 0.46)[b]	0.002	300
Bromodichloro-methane (BDCM)	Kidney, Developing fetus	Renal cytomegaly	17.9	0.02	1,000
Cadmium (Cd)	Kidney	Proteinuria	Not established (NOAEL is 0.005 [water], 0.01 [food])	0.0005 (water) 0.001 (food)	10
Carbon tetrachloride (CCl4)	Liver	Lesions (mild centrilobular vacuolization, increased serum sorbitol dehydrogenase activity)	7.1	0.0007	1,000
Chromium III (insoluble salts) (Cr III)	Liver, spleen	Decreased organ weights	Not established (NOAEL is 1,468)	1.5	900
Chromium VI (Cr VI)	No observed effect	No observed effect	Not established (NOAEL is 2.5)	0.003	1,000
Dichloroacetic Acid (DCA)	Reproductive system, Developing fetus, Liver, Brain	Lesions in the testes, cerebrum, cerebellum, liver	12.5	0.004	3,000
Mercury (based on mercuric chloride) (Hg)	Kidney	Autoimmune glomerulonephritis	0.317	0.0003	1,000

TABLE B-1 cont.

Chemical	Primary System/Organ Affected	Primary Noncancer Effect	Primary Effect LOAEL (mg/kg-day)	Oral RfD (mg/kg-day)	Oral RfD Combined Uncertainty Factor/Modifying Factor
Nickel (soluble salts) (Ni)	Kidney, liver, spleen	Decreased body and organ weights	50	0.02	300
Nitrate (NO_3)	Blood	Methemoglobinemia	1.8-3.2	1.6	1
Nitrite (NO_2)	Blood	Methemoglobinemia	11-20 ppm	0.1	10
Polychlorinated Biphenyls (PCBs) (Arochlor 1016)	Reproductive system, Brain	Reduced birth weights	0.028	0.00007	100
Trichloroethylene[a] (TCE)	Liver, kidney, and developing fetus	Disruption of cellular processes through multiple metabolites and mechanisms in liver, kidney, fetus	1.0	0.0003	3,000
Uranium (soluble salts) (U)	Kidney	Initial body weight loss, moderate nephrotoxicity	2.8	0.003	1,000
Zinc (Zn)	Blood	47% decrease in erythocyte superoxide dismutase concentration (adult females after 10-week exposure)	0.91	0.3	3

[a] Source: U.S. EPA (2005c). The exception is the RfD for trichloroethylene, taken from U.S. EPA (2001c).
[b] The benchmark dose is a BMD_{10} value, i.e., the dose at the 95% confidence limit of the dose-response model corresponding to a 10% increase in incidence of these effects compared with controls.

Acronyms and abbreviations are defined as follows: LOAEL = lowest-observed-adverse-effect level; mg/kg-day = milligram per kilogram body weight per day; NOAEL = no-observed-adverse-effect level; RfD = reference dose.

TABLE B-2

Primary Effects from Inhalation Exposures[a]

Chemical	Primary System/ Organ Affected	Primary Noncancer Effect	LOAEL for Primary Effect (mg/m^3)	Inhalation RfC (mg/m^3)	Inhalation RfC Combined Uncertainty Factor/ Modifying Factor
Arsenic (inorganic)	Not established	No observed effect	Not established	Not established	Not established
Beryllium	Lung	Beryllium sensitization, progression to chronic beryllium disease	0.0002	0.00002	10
Cadmium	Not established	No observed effect	Not established	Not established	Not established
Chromium III (insoluble salts)	Not established	No observed effect	Not established	Not established	Not established
Chromium VI (dissolved aerosols, chromic acid mists)	Respiratory system	Atrophy of the nasal septum	0.000714	0.000008	90
Chromium VI (particulates)	Respiratory system	Lactate dehydrogenase in bronchoalveolar lavage fluid, indicating inflammation and injury	Not established (benchmark dose is 0.034)[b]	0.0001	300
Copper	Not established	No observed effect	Not established	Not established	Not established
Mercury	Central nervous system	Hand tremor, increases in memory disturbance	0.009	0.0003	30
Nickel (soluble salts)	Not established	No observed effect	Not established	Not established	Not established
Nitrate	Not established	No observed effect	Not established	Not established	Not established

TABLE B-2 cont.

Chemical	Primary System/ Organ Affected	Primary Noncancer Effect	LOAEL for Primary Effect (mg/m^3)	Inhalation RfC (mg/m^3)	Inhalation RfC Combined Uncertainty Factor/ Modifying Factor
Nitrite	Not established	No observed effect	Not established	Not established	Not established
Trichloroethylene[a]	Central nervous system, liver, and endocrine system	Adverse effects on central nervous system	38	0.04	1,000
Uranium (soluble salts)	Not established	No observed effect	Not established	Not established	Not established
Zinc	Not established	No observed effect	Not established	Not established	Not established

[a] Source: U.S. EPA (2005c). The exception is the RfC for trichloroethylene, taken from U.S. EPA (2001c).
[b] The benchmark dose is a BMD_{10} value, i.e., the dose at the 95% confidence limit of the dose-response model corresponding to a 10% increase in incidence of these effects compared with controls.

Acronyms and abbreviations are defined as follows: LOAEL = lowest-observed-adverse-effect level. In some cases this reflects an adjusted value (e.g., for beryllium, the study LOAEL was adjusted to account for inhalation rate and days exposed); mg/m^3 = milligram per cubic meter (air); RfC = reference concentration.

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TABLE B-3

Comparison of Selected Secondary Effect Levels to Reference Doses for Oral Exposures[a]

Chemical	Type of Level	Value (mg/kg-day)	Ratio to RfD	Study Basis	Organ/System Effect	Reference
Arsenic (inorganic)	RfD	0.0003	1	NOAEL of 0.0008 mg/kg-day; LOAEL of 0.014 mg/kg-day; human study; UF 3; MF 1 (inorganic)	Skin - hyperpigmentation, keratosis; possible vascular complications	U.S. EPA, 2005c
	Lowest human NOAEL	0.0004	1.3	Chronic drinking water study, continuous exposure (inorganic)	Skin – lesions; abnormal nerve conduction	Cebrian et al., 1983 (cited in U.S. EPA, 2005c and ATSDR, 2000a)
	Lowest human NOAEL	0.0004	1.3	Chronic drinking water study; continuous exposure (pentavalent arsenic)	Skin – pigmentation changes, hyperkeratosis; GI system – nausea, diarrhea	Cebrian et al., 1983 (cited in ATSDR, 2000a)
	Lowest human LOAEL	0.0008	2.7	Chronic drinking water study (test compound not reported)	Skin - hyperpigmentation, hyperkeratosis	Foy et al., 1992 (cited in ATSDR, 2000a)
	Lowest animal NOAEL	0.025	83	Rat gavage study (7 months) (arsenic solution)	No increased embryonic effects; infrequent slight expansion of ventricles of the cerebrum, renal pelvis, urinary bladder	Nadeenko et al. 1978 (cited in U.S. EPA, 2005c and ATSDR, 2000a)
	Lowest animal LOAEL	0.8	2670	Dog oral study (26 weeks) (trivalent)	Liver - mild increase in serum ALT/AST	Neiger and Osweiler, 1989 (cited in ATSDR, 2000a)

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TABLE B-3 cont.						
Chemical	Type of Level	Value (mg/kg-day)	Ratio to RfD	Study Basis	Organ/System Effect	Reference
Beryllium	RfD	0.002	1	BMD_{10} of 0.46 mg/kg-day; dog oral study; in food; UF 300; MF 1 (sulfate tetrahydrate)	Multiple target organs; small intestinal lesions.	U.S. EPA, 2005c
	Lowest human NOAEL	Not reported	NA	NA	NA	NA
	Lowest human LOAEL	Not reported	NA	NA	NA	NA
	Lowest animal NOAEL	0.7	350	Rat oral study; in water (3 years) (sulfate)	Various organ systems (e.g., cardiovascular, endocrine, hepatic, renal, respiratory)	Schroeder and Mitchener, 1975 (cited in ATSDR, 2002c)
	Lowest animal NOAEL	0.7	350	Rat oral study; drinking water (91 days) (sulfate)	Whole body - no effects	Freundt and Ibrahim, 1990 (cited in ATSDR, 2002c)
	Lowest animal LOAEL	12	6,000	Dog oral study; in food (172 weeks) (sulfate)	GI system – ulcerative, inflammatory lesions; hematopoetic system - erythroid hypoplasia of bone marrow; whole body - weight loss, increased mortality	Morgareidge et al., 1976 (cited in ATSDR, 2002c)

TABLE B-3 cont.						
Chemical	Type of Level	Value (mg/kg-day)	Ratio to RfD	Study Basis	Organ/System Effect	Reference
Cadmium	RfD – water	0.0005	1	NOAEL of 0.005 mg/kg-day (water); human study; UF 10; MF 1	Kidney - proteinuria (note: supporting data have been derived from many animal and human studies, renal effects, proteinuria, and calcium pharmacokinetic parameters)	Data from U.S. EPA, 2005d (effect type note from RAIS, 1991)
	RfD – food	0.001	1	NOAEL of 0.01 mg/kg-day (food); human study; UF 10; MF 1	Kidney - proteinuria (note: supporting data have been derived from many animal and human studies, renal effects, proteinuria, and calcium pharmacokinetic parameters)	Data from U.S. EPA, 2005c (effect type note from RAIS, 1991)
Cadmium	Lowest human NOAEL	0.0021	2.1	Chronic lifetime exposure in food (test compound not reported)	Kidney - no effects	Nogawa et al., 1989 (cited in ATSDR, 1999b)
	Lowest human LOAEL	0.0078	7.8	Chronic oral study (25 years) (inorganic)	Kidney - renal tubule interstitial lesions	Shiwen et al., 1990 (cited in ATSDR, 1999b)
	Lowest animal NOAEL	0.0081	16	Rat chronic oral study (5 months); in water (chloride)	Whole body - no effects	Perry et al., 1989 (cited in ATSDR, 1999b)
	Lowest animal LOAEL	0.001	2	Rat chronic oral study (18 months); in water (acetate)	Cardiovascular system-hypertension; increase in systolic blood pressure	Kopp et al., 1982 (cited in ATSDR, 1999b)

TABLE B-3 cont.						
Chemical	Type of Level	Value (mg/kg-day)	Ratio to RfD	Study Basis	Organ/System Effect	Reference
Carbon tetrachloride	RfD	0.0007	1	NOAEL of 0.71 mg/kg-day; LOAEL of 7.1 mg/kg-day; rat gavage study (12 weeks); UF 1,000; MF 1	Liver - lesions (mild centrilobular vacuolization and increases in serum sorbitol dehydrogenase activity)	U.S. EPA, 2005c
	Lowest human NOAEL	Not reported	NA	NA	NA	NA
	Lowest human LOAEL	Not reported	NA	NA	NA	NA
	Lowest animal NOAEL	1.0	1,430	Rat gavage study (12 weeks)	Liver - substantially elevated sorbitol dehydrogenase; mild centrilobular vacuolization	Bruckner et al., 1986 (cited in ATSDR, 2003a)
	Lowest animal LOAEL	10	14,300	Rat gavage study (12 weeks)	Liver - substantially elevated sorbitol dehydrogenase; mild centrilobular vacuolization	Bruckner et al., 1986 (cited in ATSDR, 2003a)

TABLE B-3 cont.						
Chemical	Type of Level	Value (mg/kg-day)	Ratio to RfD	Study Basis	Organ/System Effect	Reference
Chromium III (insoluble salts)	RfD	1.5	1	NOAEL of 1,468 mg/kg-day; rat chronic oral study; UF 100; MF 10 (chronic oxide)	Liver and spleen – decreased organ weights	U.S. EPA, 2005c
	Lowest human NOAEL	Not reported	NA	NA	NA	NA
	Lowest human LOAEL	Not reported	NA	NA	NA	NA
	Lowest animal NOAEL	0.46	0.31	Rat chronic drinking water study (2-3 years) (trivalent)	Cardiovascular system, liver, kidney, whole body - no effects	Schroeder et al., 1965 (cited in ATSDR, 2000b)
	Lowest animal LOAEL	5.0	3.3	Mouse drinking water study (12 weeks) (trivalent)	Reproductive system - increased testes, decreased preputial gland weights; decreased number of implantations and viable fetuses; increased ovarian, decreased uterine weights; whole body - decrease in body weight gain	Elbetieha and Al-Hamood, 1997 (cited in ATSDR, 2000b)

TABLE B-3 cont.						
Chemical	Type of Level	Value (mg/kg-day)	Ratio to RfD	Study Basis	Organ/System Effect	Reference
Chromium VI	RfD	0.003	1	NOAEL of 2.5 mg/kg-day; rat chronic drinking water study (1 year); UF 300; MF 3 (potassium chromate)	No effects	U.S. EPA, 2005c
	Lowest human NOAEL	Not reported	NA	NA	NA	NA
Chromium VI	Lowest human LOAEL	0.57	190	Unspecified environmental exposure (hexavalent)	GI system - oral ulcers, diarrhea, vomiting abdominal pain; hematopoetic system – leukocytosis, immature neutrophils	Zhang and Li, 1987 (cited in ATSDR, 2000b)
	Lowest animal NOAEL	1.1	367	Mouse oral study, in food (9 weeks) (hexavalent)	Liver - cytoplasmic vacuolization of hepatocytes	NTP, 1996 (cited in ATSDR, 2000b)
	Lowest animal LOAEL	3.5	1170	Mouse oral study, in food (9 weeks) (hexavalent)	Liver - cytoplasmic vacuolization of hepatocytes	NTP, 1996 (cited in ATSDR, 2000b)

TABLE B-3 cont.						
Chemical	Type of Level	Value (mg/kg-day)	Ratio to RfD	Study Basis	Organ/System Effect	Reference
Mercury	RfD	0.0003	1	LOAEL of 0.317 mg/kg-day; rat study; UF 1,000; MF 1 (mercuric chloride)	Kidney - autoimmune glomerulonephritis; assumes the oral absorption of divalent mercury is 7% and absorption from subcutaneous exposure is 100%	U.S. EPA, 2005c
	Lowest human NOAEL	0.0005	1.67	Oral study (methylmercury)	Developmental - no effects	Myers et al., 1997 (cited in ATSDR, 1999c)
	Lowest human LOAEL	0.0012	4	Oral study, food (methylmercuric chloride)	Developmental - delayed walking, abnormal motor scores	Cox et al., 1989 (cited in ATSDR, 1999c)
	Lowest animal NOAEL	0.05	167	Rat oral study, food (52 days) (methylmercuric chloride)	Developmental – increased incidence of eye defects in fetuses	Khera and Tabacova, 1973 (cited in ATSDR, 1999c)
	Lowest animal LOAEL	0.05	167	Monkey oral study, water (328-907 days) (methylmercury hydroxide)	Developmental – impaired visual recognition memory in offspring	Gunderson et al., 1988 (cited in ATSDR, 1999c)

TABLE B-3 cont.						
Chemical	Type of Level	Value (mg/kg-day)	Ratio to RfD	Study Basis	Organ/System Effect	Reference
Nickel (soluble salts)	RfD	0.02	1	NOAEL of 5 mg/kg-day; LOAEL of 50 mg/kg-day; rat study; in food; UF 300; MF 1	Multiple target organs; changes in body and organ weights	U.S. EPA, 2005c
	Lowest human NOAEL	0.02	1	Oral study; water (178 days) (sulfate)	Dermal - no effects	Santucci et al., 1994 (cited in ATSDR, 2003b)
	Lowest human LOAEL	Not reported	NA	NA	NA	NA
	Lowest animal NOAEL	0.97	48	Rat oral study; water (28 days) (chloride)	Hematopoetic system - no effects; liver - no effects	Weischer et al., 1980 (cited in ATSDR, 2003b)
	Lowest animal LOAEL	0.23	12	Rat oral study; water (28 days) (chloride)	Whole body - decreased body weight gain; metabolic system effects	Weischer et al., 1980 (cited in ATSDR, 2003b)

TABLE B-3 cont.						
Chemical	Type of Level	Value (mg/kg-day)	Ratio to RfD	Study Basis	Organ/System Effect	Reference
Nitrate	RfD	1.6	1	NOAEL of 1.6 mg/kg-day; human study; LOAEL of 1.8-3.2 mg/kg-day; (infants, drinking water in formula); UF 1; MF 1	Hematopoetic system - methemoglobinemia	U.S. EPA, 2005c
	Lowest human NOAEL	3.7	2.3	Oral study, 1- to 6-month-old infants; nitrate in formula	Hematopoetic system - no methemoglobinemia clinical signs	Simon et al., 1964 (cited in U.S. EPA, 2005c)
	Lowest human LOAEL	3.2	2	Oral study, 8-day to 5-month-old infants; nitrate in formula	Hematopoetic system - cyanosis, methemoglobinemia	Bosch et al., 1950 (cited in U.S. EPA, 2005c)
	Lowest animal NOAEL	20	12	Oral rat drinking water study (2 years) (sodium nitrite)	Respiratory system - dilated bronchi, fibrosis, emphysema	Shuval and Gruener, 1972 (cited in U.S. EPA, 2005c)
	Lowest animal LOAEL	60	38	Rat oral study, drinking water (2 years) (sodium nitrite)	Lung – dilated bronchi, fibrosis and emphysema, Circulatory/cardiovascular system - fibrosis, degenerative foci	Shuval and Gruener, 1972 (cited in RAIS, 1995)

TABLE B-3 cont.						
Chemical	Type of Level	Value (mg/kg-day)	Ratio to RfD	Study Basis	Organ/System Effect	Reference
Nitrite	RfD	0.1	1	NOEL of 1.0 mg/kg-day; LOAEL of 1.1-2.0 mg/kg-day; human study; UF 1; MF 10 (from nitrate)	Hematopoetic system – methemoglobinemia	U.S. EPA, 2005c
	Lowest human NOAEL	1.0	10	Oral study, infants, nitrate in formula	Hematopoetic system - methemoglobinemia above 10%	Walton, 1951 (cited in U.S. EPA, 2005c)
	Lowest human LOAEL	Not reported	NA	NA	NA	NA
Trichloro-ethylene	RfD	0.0003	1	LOAEL of 1.0 mg/kg-day; subchronic mice and rats studies (liver effects); UF 3000	Various effects - liver; kidney; developing fetus	U.S. EPA, 2001c
	Lowest human NOAEL	Not reported	NA	NA	NA	NA
	Lowest human LOAEL	Not reported	NA	NA	NA	NA
	Lowest animal NOAEL	18	60,000	Mouse drinking water study (6 months)	GI - gas pockets in the intestinal coating; blood in the intestines	Tucker et al., 1982 (cited in ATSDR, 1997c)
	Lowest animal LOAEL	0.18	600	Rat drinking water study, gestational (3 months)	Developmental - increased fetal heart abnormalities	Dawson et al., 1993 (cited in ATSDR, 1997c)

TABLE B-3 cont.						
Chemical	Type of Level	Value (mg/kg-day)	Ratio to RfD	Study Basis	Organ/System Effect	Reference
Uranium (soluble salts)	RfD	0.003	1	LOAEL of 2.8 mg/kg-day, rabbit dietary study; UF 1,000; MF 1 (30 days) (uranyl nitrate hexahydrate; soluble salt)	Kidney - moderate nephrotoxicity; whole body - initial body weight loss	U.S. EPA, 2005c
	Lowest human NOAEL	Not reported	NA	NA	NA	NA
	Lowest human LOAEL	Not reported	NA	NA	NA	NA
	Lowest animal NOAEL	0.06	20	Rat drinking water study (91 days) (uranyl nitrate hexahydrate)	Endocrine system - multi-focal reduction of follicular size; increased epithelial height in thyroid; decreased amount and density of colloid in males only	Gilman et al., 1998a (cited in ATSDR, 1999d)
	Lowest animal LOAEL	0.05	17	Rabbit drinking water study (91 days) (uranyl nitrate hexahydrate)	Kidney - anisokaryosis, nuclear vesiculation	Gilman et al., 1998b (cited in ATSDR, 1999d)

TABLE B-3 cont.

Chemical	Type of Level	Value (mg/kg-day)	Ratio to RfD	Study Basis	Organ/System Effect	Reference
Zinc	RfD	0.3	1	LOAEL of 1.0 mg/kg-day; human dietary supplement study; UF 3; MF 1	Hematopoetic system - 47% decreased ESOD concentration (in adult females after 10-week exposure)	Yadrick et al., 1989 (cited in U.S. EPA, 2005c)
	Lowest human NOAEL	0.06	0.2	Dietary supplement study (11 weeks) (aspartate)	Developmental - no effects	Kynast and Saling, 1986 (cited in ATSDR, 2003c)
	Lowest human LOAEL	0.71	2.4	Dietary supplement study (12 weeks) (gluconate)	Liver - decreased serum HDL-cholesterol[b]	Black et al., 1988 (cited in ATSDR, 2003c)
	Lowest human LOAEL	0.71	2.4	Dietary supplement study (6 weeks) (gluconate)	Hematopoetic system - decreased ESOD activity	Fischer et al., 1984 (cited in ATSDR, 2003c)
	Lowest animal NOAEL	3.5	12	Rat gavage study; in water (20 months) (chloride)	Reproductive effects - decreased live pups per litter	Khan et al., 2001 (cited in ATSDR, 2003c)
	Lowest animal LOAEL	0.5	1.7	Mouse oral study, in water (60 days) (acetate)	Nervous system - increase in latency in inhibitory avoidance test	De Oliveira et al., 2001 (cited in ATSDR, 2003c)

[a] This table presents information for 15 chemicals selected for study at a contaminated site. The form of the chemical or compound used in the toxicity study that served as the basis for the indicated level is given in parentheses; where not listed here, the chemical itself was identified as the test chemical. Selected acronyms are defined as follows; others (e.g., agency acronyms) are included in the notation at the front of this report. ALT/AST = alanine aminotransferase/aspartate aminotransferase; BMD_{10} = benchmark dose, at the 95% confidence limit of the dose-response model corresponding to a 10% increase in incidence of the effect compared with the control; ESOD = erythocyte superoxide dismutase; GI = gastrointestinal system; HDL = high-density lipid; LOAEL = lowest-observed-adverse-effect level; MF = modifying factor; mg/kg-day = milligram per kilogram per day; NA = not available/not applicable; NOAEL = no observed adverse effect level; RfD = reference dose; UF = uncertainty factor.

[b] Low levels of low-density lipoprotein (LDL) cholesterol put a person at a high risk of heart disease. Taken from The American Heart Association "What are Healthy Levels of Cholesterol?" See http://www.americanheart.org/presenter.jhtml?identifier=183.