EPA/600/R-06/013F
August 2007

Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

in collaboration with

U.S. Department of Energy Argonne National Laboratory
Environmental Assessment Division
Argonne, IL 60439

NOTICE

The U.S. Environmental Protection Agency through its Office of Research and Development conducted, and funded research described here under two collaborative Interagency Agreements, Numbers DW89921662 and DW89939210, with the Department of Energy from 2001 to 2006. It has been subjected to the Agency's peer and administrative review and has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

ABSTRACT

Public interest in the health impacts of environmental chemical exposures and their interactions with other stressors continues to grow with increased information about exposures to multiple chemicals in air, water and soil from different sources. However, population vulnerability factors, such as diet, behaviors, genetic traits, economic status and social characteristics are often not considered. Cumulative risk assessment may be thought of as a population-based analysis, characterization and possible quantification of the combined risks to health or the environment from multiple route exposures to multiple agents or stressors. This current report serves as a resource document for identifying specific elements of and approaches for implementing cumulative risk assessments. This report is not a regulatory document and is not guidance but rather a presentation of concepts, methods and data sources. It is designed to assist EPA's development of specific approaches and cumulative risk guidance for use by its Program Offices and Regions. It is intended as a resource for EPA scientists and others in the broader risk assessment community with an interest in locating data and approaches relevant to cumulative risk assessment. This report focuses on two areas: initiating factors for a cumulative risk assessment with procedures for data collection and organization; and technical approaches for assessing and characterizing human health risks associated with a subset of cumulative risk issues (i.e., multiple chemicals, exposures and effects). Schematics are shown for evaluating data, profiling the population of concern, grouping chemicals into integrated exposure and toxicity groups, performing toxicity assessments and conducting cumulative risk characterizations. Issues discussed include toxicological interactions, pharmacokinetics, multiple toxic effects, epidemiologic methods, biomonitoring data, the temporal nature of exposures and environmental chemical transformations. Articulation of variability and uncertainty is stressed as part of the final Risk Characterization.

Preferred citation:
U.S. EPA. 2007. Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document. U.S. Environmental Protection Agency, National Center for Environmental Assessment, Cincinnati, OH. EPA/600/R-06/013F.

TABLE OF CONTENTS

TABLE OF CONTENTS cont.

TABLE OF CONTENTS cont.

TABLE OF CONTENTS cont.

TABLE OF CONTENTS cont.

LIST OF TABLES

LIST OF FIGURES

LIST OF FIGURES cont.

LIST OF FIGURES cont.

LIST OF TEXT BOXES

LIST OF TEXT BOXES cont.

LIST OF ABBREVIATIONS

The main acronyms and abbreviations used in this 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.

atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	lower confidence limit on BMD
BP	boiling point
°C	degrees Celsius or centigrade
Cd	Cadmium
CDC	Centers for Disease Control and Prevention
CEP	Cumulative Exposure Project
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CHI	cumulative hazard index
Cl_2	free chlorine
DBP	disinfection byproduct
DCA	1,1-dichloroethane
DDT	dichlorodiphenyltrichloroethane
DNA	deoxyribonucleic acid
DNAPL	dense nonaqueous phase liquid
DOE	U.S. Department of Energy
EFH	Exposure Factors Handbook
EPA	U.S. Environmental Protection Agency
ETS	environmental tobacco smoke
foc	fraction of organic carbon
FQPA	Food Quality Protection Act
GEP	good engineering practice
GIS	geographic information system
Hg	mercury
HQ	hazard quotient
ICED	Index Chemical Equivalent Dose
IRIS	Integrated Risk Information System (EPA database)
IUR	inhalation unit risk

LIST OF ABBREVIATIONS cont.

Kd	soil-water partition coefficient
K_H	Henry's constant
Kow	octanol-water partition coefficient
Ksp	solubility product
L	liter
LOAEL	lowest-observed-adverse-effect level
m^3	cubic meter
mg	milligram
mg/kg	milligram per kilogram
mg/kg-day	milligram per kilogram body weight per day
mm	millimeters
MOA	mode of action
mol	moles
MP	melting point
NAS	National Academy of Sciences
NCEA	National Center for Environmental Assessment, EPA
NHEXAS	National Human Exposure Assessment Survey
NOAEL	no observed adverse effect level
NRC	National Research Council (NAS)
OPP	Office of Pesticide Programs
ORD	Office of Research and Development (EPA)
OSWER	Office of Solid Waste and Emergency Response
PAHs	polycyclic aromatic hydrocarbons
Pb	lead
PBPK	physiologically-based pharmacokinetic (model)
PBTK	physiologically-based toxicokinetic
PCBs	polychlorinated biphenyls
PM2.5	particulate matter with a diameter of 2.5 μm or less
PM10	particulate matter with a diameter of 10 μm or less
ppb	parts per billion
ppm	parts per million
RAGS	Risk Assessment Guidance for Superfund (EPA)
RAPIDS	Regional Air Pollutant Inventory Development System
RfC	reference concentration
RfD	reference dose
RPF	relative potency factor
RFV	reference value

LIST OF ABBREVIATIONS cont.

Sw	solubility in water
TCDD	tetrachlorodibenzo(p)dioxin
TCE	trichloroethylene
TD	toxicodynamics
TEQ	toxicity equivalents
TK	toxicokinetics
TPA	tris(2-ethylhexyl) phosphate
TSP	total suspended particulates
TTD	target organ toxicity doses
UF	uncertainty factor
μg	microgram
μm	micrometer
VOC	volatile organic compounds
VP	vapor pressure
WOE	weight of evidence

PREFACE

This report was developed as a collaborative 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) and the Department of Energy's Argonne National Laboratory. It offers information that can be used to implement basic cumulative risk assessment concepts within the framework set forth by EPA. This current report serves as a resource document for identifying specific elements of and approaches for implementing cumulative risk assessments. This report is not a regulatory document and is not guidance but rather a presentation of concepts, methods and data sources. It is designed to assist EPA's development of specific approaches and cumulative risk guidance for use by its Program Offices and Regions. It is intended as a resource for EPA scientists and others in the broader risk assessment community with an interest in locating data and approaches relevant to cumulative risk assessment. The aim is to illustrate approaches and resources that can be used to more explicitly assess human health cumulative risks from multiple route exposures to multiple chemicals found at sites or within communities. 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 which could be exposed over time, multiple health effects and toxicological interactions among chemicals. The overall goal of using cumulative risk assessment 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. External peer review included two categories of comments that were collected between March and July 2006: (1) comments from an independent peer review panel, organized and implemented by Eastern Research Group (ERG) under EPA Contract No 68-C-02-060, in a meeting open to the public on May 25–26, 2006, in Cincinnati, Ohio and (2) public comments using an E-docket during a 45 day public comment period from March 31-May 15, 2006. The public comments received by EPA were issued to the Peer Review panel members prior to the May 2006 review meeting for their consideration in making comments and recommendations to EPA. Information concerning the peer review meeting results can be found online at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=149983.

AUTHORS, CONTRIBUTORS AND REVIEWERS

This research was sponsored by the U.S. Environmental Protection Agency (EPA), Office of Research and Development, National Center for Environmental Assessment—Cincinnati Division (NCEA). Through an interagency agreement, NCEA researchers collaborated with scientists from the Department of Energy's Argonne National Laboratory to conduct this research and to author this report. These individuals are listed below.

AUTHORS

National Center for Environmental Assessment, U.S. EPA, Cincinnati, OH
Richard C. Hertzberg (Project Lead, Retired)
Linda K. Teuschler
Glenn E. Rice
John C. Lipscomb
J. Michael Wright
Jason C. Lambert
Anthony Fristachi

Argonne National Laboratory, U.S. Department of Energy, Argonne, IL
Margaret MacDonell (Project Lead)
James Butler
Young-Soo Chang
Heidi Hartmann
John Peterson
Kurt Picel

Tetra Tech EM, Inc., Dallas, TX
Shanna Collie
Shannon Garcia
Alan Johns
Camarie Perry

ENVIRON Corporation, Emeryville, CA
Lynne Haroun

CONTRIBUTORS AND REVIEWERS

Gary Bangs
U.S. Environmental Protection Agency
National Center for Environmental Assessment
Washington, DC

Edward Bender (retired)
U.S. Environmental Protection Agency
Office of Assistant Administrator
Office of Science Advisor
Washington, DC

Michael Callahan
U.S. Environmental Protection Agency
Region 6
Dallas, TX

James Carlisle (Expert Panel)
California EPA
Office of Environmental Health Hazard Assessment
Meadow Vista, CA

David Carpenter (Expert Panel)
Institute for Health and the Environment
University of Albany
Rensselaer, NY

Paul Chrostowski (Expert Panel)
CPF Associates, Inc.
Takoma Park, MD

David Cooper
U.S. Environmental Protection Agency
Office of Solid Waste and Emergency Response
Washington, DC

Audrey Galizia
U.S. Environmental Protection Agency
National Center for Environmental Assessment
Cincinnati, OH

Ihor Hlohowskyj
U.S. Department of Energy
Argonne National Laboratory Team
Argonne, IL

Pat Jennings
U.S. Environmental Protection Agency
Office of Water
Washington, DC

Jeremy Johnson
U.S. Environmental Protection Agency
Region 7
Kansas City, KS

Kannan Krishnan (Chair, Expert Panel)
Human Toxicology Research Group
University of Montreal
Canada

Sarah Levinson
U.S. Environmental Protection Agency
Region 1
Boston, MA

Margaret McDonough
U.S. Environmental Protection Agency
Region 1
Boston, MA

Chuck Nace
U.S. Environmental Protection Agency
Region 2
New York, NY

Michael Posson
ENVIRON
Emeryville, CA

Kaitlin Prieur
Tetra Tech EM, Inc.
Dallas, TX

CONTRIBUTORS AND REVIEWERS cont.

Stig Regli
U.S. Environmental Protection Agency
Office of Water
Washington, DC

Jon Reid
U.S. Environmental Protection Agency
National Center for Environmental Assessment
Cincinnati, OH

Libby Stull
U.S. Department of Energy
Argonne National Laboratory Team
Argonne, IL

Robert Sullivan
U.S. Department of Energy
Argonne National Laboratory Team
Argonne, IL

David Tomasko
U.S. Department of Energy
Argonne National Laboratory Team
Argonne, IL

Nga Tran (Expert Panel)
ExPonent, Inc.
Washington, DC

EXECUTIVE SUMMARY

ES.1. BACKGROUND

Public interest in and awareness of the health impacts of environmental chemical exposures and their interactions with other stressors continues to grow as more information is assembled about exposures to multiple chemicals in air, water and soil from different sources. Environmental Protection Agency (EPA) has responded to increasing requests for ways to understand and evaluate the combined impacts of these conditions by preparing a set of reports on various aspects of cumulative risk assessment. The EPA's *Framework for Cumulative Risk Assessment* (herein referred to as the *Framework*) defines the general concepts and considerations for these assessments (U.S. EPA, 2003a), and earlier reports laid a broad foundation for the initial Planning and Scoping phase needed to conduct a cumulative risk assessment (U.S. EPA, 1997a, 2002a). This report is linked to, and relies upon these documents, as well on several key EPA guidance documents, as illustrated by the examples in Figure ES-1. This current report serves as a resource document for identifying specific elements of and approaches for implementing cumulative risk assessments. This report is not a regulatory document and is not guidance but rather a presentation of concepts, methods and data sources. It is designed to assist EPA's development of specific approaches and cumulative risk guidance for use by its Program Offices and Regions. It is intended as a resource for EPA scientists and others in the broader risk assessment community with an interest in locating data and approaches relevant to cumulative risk assessment.

The *Framework* defines cumulative risk as the combined risks from aggregate exposures (i.e., multiple route exposures) to multiple agents or stressors, where agents or stressors may include chemicals, as well as biological or physical agents (e.g., noise, nutritional status), or the absence of a necessity such as habitat (U.S. EPA, 2003a). Cumulative risk assessment, then, is an analysis, characterization and possible quantification of the combined risks to health or the environment from multiple agents or stressors. Other important aspects of cumulative risk assessment include a population focus, emphasis on stakeholder involvement, consideration of population vulnerabilities, and a focus on both human health and ecology. Areas of vulnerability articulated in the *Framework* for human and biological ecosystems, communities and populations include susceptibility or sensitivity, differential exposure (e.g., caused by cultural practices or by living in close proximity to pollutant sources), differential preparedness (e.g., lack of disease immunizations) and differential ability to recover. Note that the conduct of a

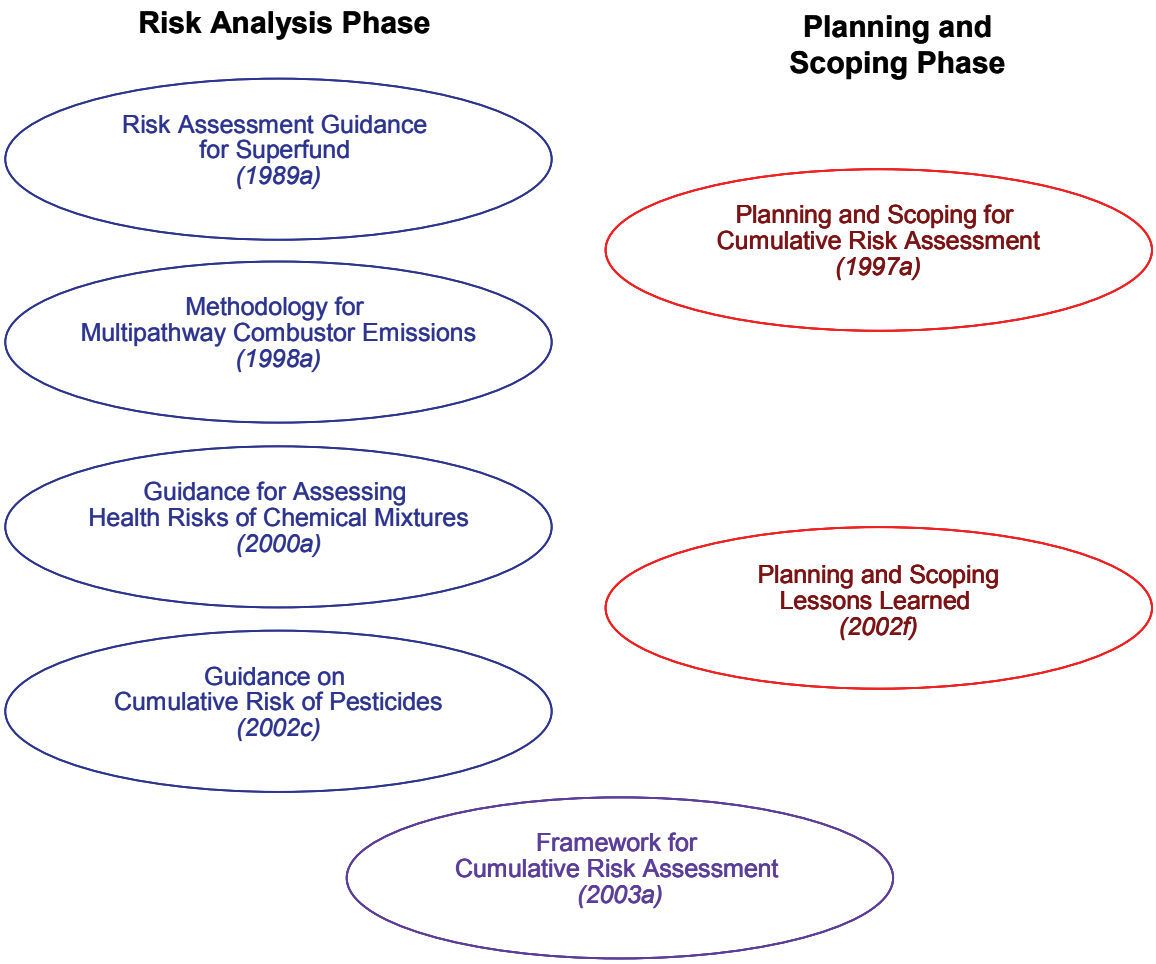


FIGURE ES-1

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

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

The *Framework* incorporates the risk assessment paradigm (NRC, 1983) within the three phases of a cumulative risk assessment that it identifies (see Figure ES-2): (1) Problem Formulation, (2) Risk Analysis and (3) Risk Characterization. Planning and Scoping, an iterative dialogue between the scientists, risk managers and stakeholders, takes place mostly during the Problem Formulation phase but may be revisited as needed during the Risk Analysis and Risk Characterization phases. The output from Risk Characterization is then used to support environmental Decision-Making. Other factors, such as economic, social and policy considerations, may enter into both the Planning and Scoping and the Decision-Making stages of the cumulative risk process. These may influence the design of the analysis or the final risk management decisions.

ES.2. SCOPE OF THIS REPORT

This report focuses on two areas: (1) concepts concerning the initiating factors for a cumulative risk assessment with procedures for data collection and organization (Chapters 1 and 2) and (2) technical approaches for assessing and characterizing health risks associated with a subset of cumulative risk issues (i.e., multiple chemicals, exposures and effects), with examples pertaining to contaminated sites, drinking water and ambient air (Chapters 3, 4 and 5). Some of the innovations proposed in this document include

- developing a description of initiating factors for a Cumulative Risk Assessment and procedures for population characterization, data collection and organization based on the initiating factors (Chapters 1 and 2);
- implementing *chemical grouping*, a potentially helpful way to scope analyses into manageable pieces to be assessed as chemical mixtures with co-occurring exposures (Chapters 3 and 4);
- approaches and data sources for evaluating the timing of exposures, including discussions of kinetics and dynamics (Chapters 3 and 4);
- integrating internal dose measurements to account for multiple route exposures (Chapters 3 and 4);
- further developing the quantitative method for the interaction-based hazard index, first introduced in the 2000 mixtures guidance document (U.S. EPA, 2000a) (Chapter 4);

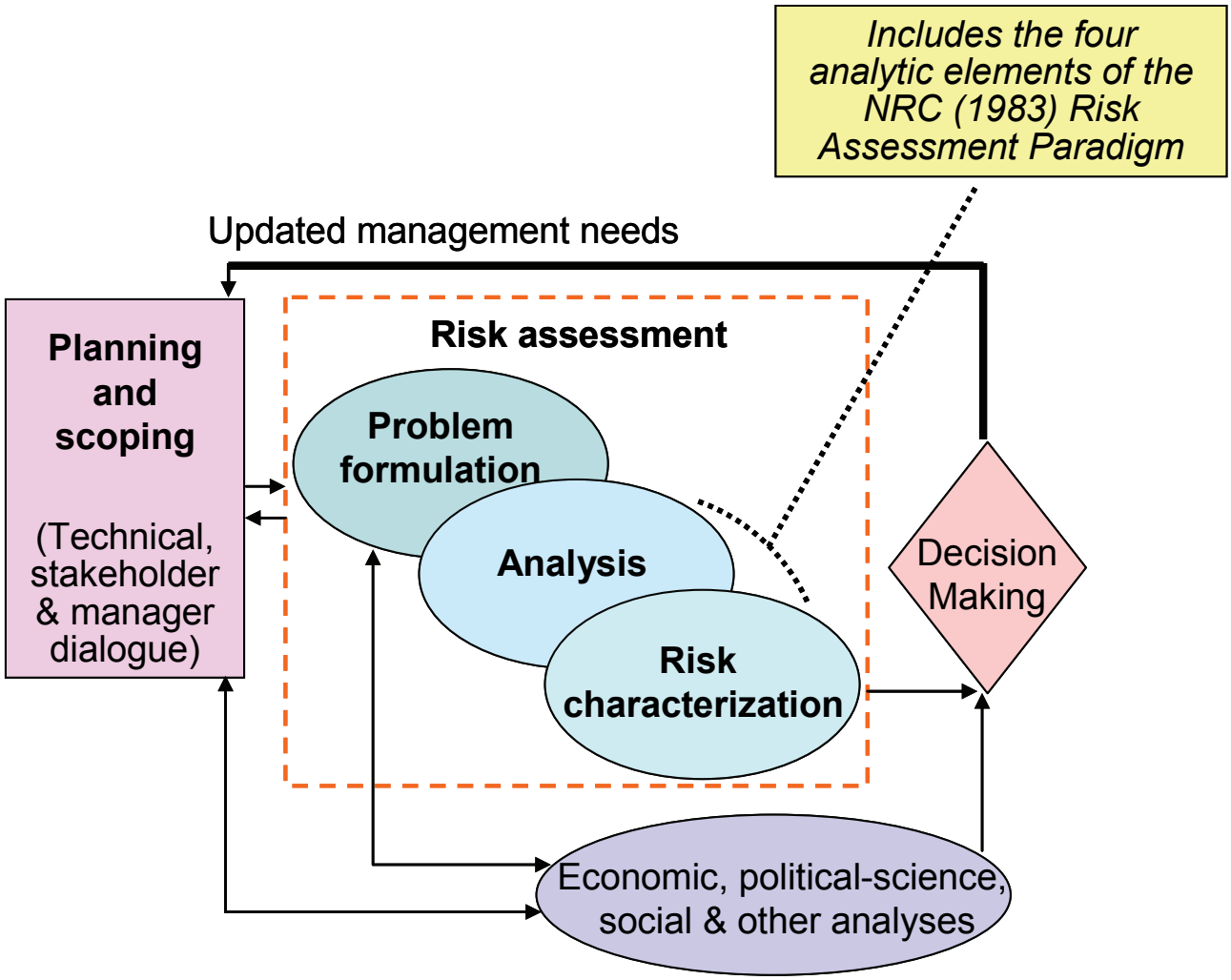


FIGURE ES-2

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

- extending the Relative Potency Factors (RFP) method to cumulate across exposure routes, an approach first presented in an earlier EPA report on drinking water disinfection by-product (DBP) mixtures (U.S. EPA, 2000e) (Chapter 4);
- integrating output from multiple effects modeling (illustrated using a categorical regression model) with the Hazard Index (HI) and response addition models to express risks for multiple health effects (Chapter 4);
- providing added detail on the cumulative HI approach used by the Superfund program (U.S. EPA, 1989a), including discussion of the impacts for risk characterization (Chapters 4 and 5);
- presentation of a method for cumulative risk characterization that considers factors unique to conduct of a Cumulative Risk Assessment, including the recognition of uncertainties in cumulative dose-response and exposure assessment (Chapter 5); and
- a general emphasis on integrating exposure and dose-response analysis (Chapters 3, 4 and 5).

This report covers only some of the many aspects of cumulative risk for human health assessment. It does not address risk management decisions and risk communication. This report also does not consider interactions with non-chemical stressors, such as noise, nor other kinds of risks, such as microbial or ecological risks. In addition, social, political and economic issues are not discussed and only some aspects of vulnerability are highlighted.

ES.3. THIS REPORT'S APPROACH TO CUMULATIVE RISK ASSESSMENT

Many situations do not have a population focus or do not involve multiple chemicals and so would not need a cumulative risk assessment. However, there are certain initiating factors that would naturally lead to conducting a cumulative risk assessment. Figure ES-3 shows these three identified initiating factors along with the data elements that may be used to conduct a cumulative risk assessment. These initiating factors are (1) multiple pollutant sources or releases, (2) elevated concentrations from environmental monitoring or biomonitoring of chemicals and (3) increased population illness in a community. Figure ES-4 illustrates the types of information that may be considered for data collection and population characterization and shows the relationship of this information to the initiating factors. It is noteworthy that traditional source-based assessments are usually initiated when chemicals are found or released into the environment from known sources. When this occurs, population vulnerability factors, such as diet, behaviors, genetic traits, economic status and social characteristics are often not included in the assessment. These traits are

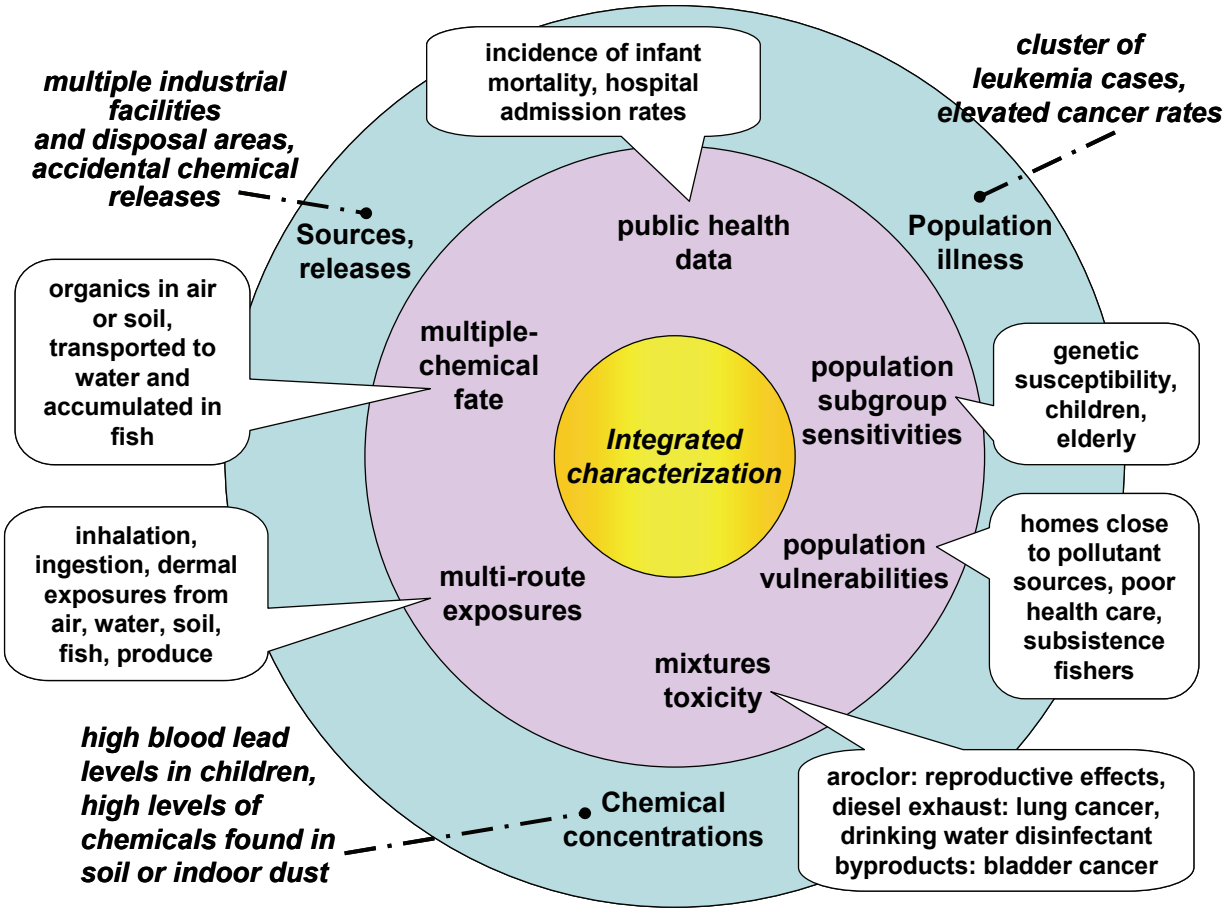


FIGURE ES-3
Example Initiating Factors and Data Elements for Cumulative Risk Analyses

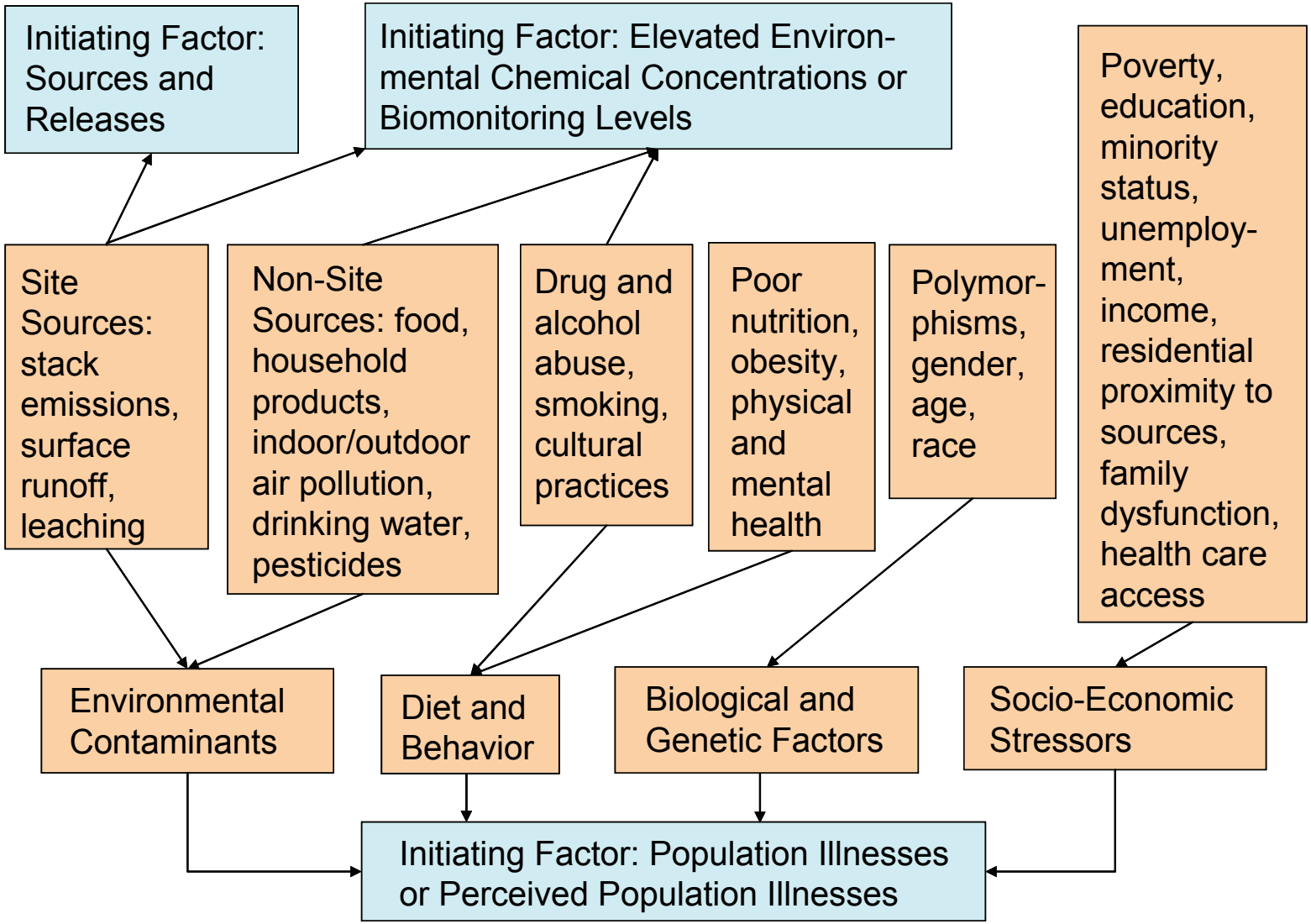


FIGURE ES-4

Variables Considered in Cumulative Risk Assessment and their Relationship to Initiating Factors

more likely to be assessed when population illness or the potential for illness are the initiating factor. Note that there may be challenges related to finding the needed expertise and collaborative partners to carry out a cumulative risk assessment when these non-traditional stressors are incorporated into an assessment. The EPA does address a few of these factors (e.g., sensitive subgroups, children, elderly), however, it may be useful to conduct additional research on analyzing health risks for vulnerable populations and to collaborate with other organizations that may have access to relevant data.

Figure ES-5 shows the key steps in a cumulative risk assessment, with a primary focus of addressing multiple chemicals, pathways, timeframes and effects in a population-based setting. These steps define the population of concern and its study area, generate a list of environmental contaminants relevant to the initiating factor and identify links between environmental chemical exposures and vulnerabilities within the population. These steps form the initial collection and organization of information to focus on the cumulative aspects of the risk assessment. These steps may not be sequential and may involve a number of iterations as the analyst examines factors related to population vulnerabilities, public health information, toxicological and epidemiologic data, completed exposure pathways, differential exposures and contact with environmental media and pollutant sources. Outputs include a population profile, a list of relevant chemicals, chemical groups for use in risk analysis and characterization and a conceptual model. Outputs may include additional epidemiologic evaluations that assess the health of the community or that examine associations between health impacts and pollutant exposures.

ES.4. EXPOSURE ASSESSMENT OF MULTIPLE CHEMICALS, EXPOSURES AND EFFECTS

In cumulative risk assessments that examine risks posed by multiple chemicals, exposure assessments evaluate a population's chemical exposures through multiple routes of exposure over time. Such assessments may encompass multiple exposure timeframes in which the timing and intensity of exposures to different chemicals are examined relative to each other. It is also important to determine whether the exposures to multiple chemicals can lead to toxicokinetic interactions[1] or toxicodynamic

[1] Toxicokinetic interactions refer to alterations in the absorption, distribution, metabolism or elimination of a toxic chemical. For example, these interactions can be mediated by the induction or inhibition of enzymes involved in xenobiotic activation or detoxification. See Appendix C U.S. EPA (2000a) for complete discussion.

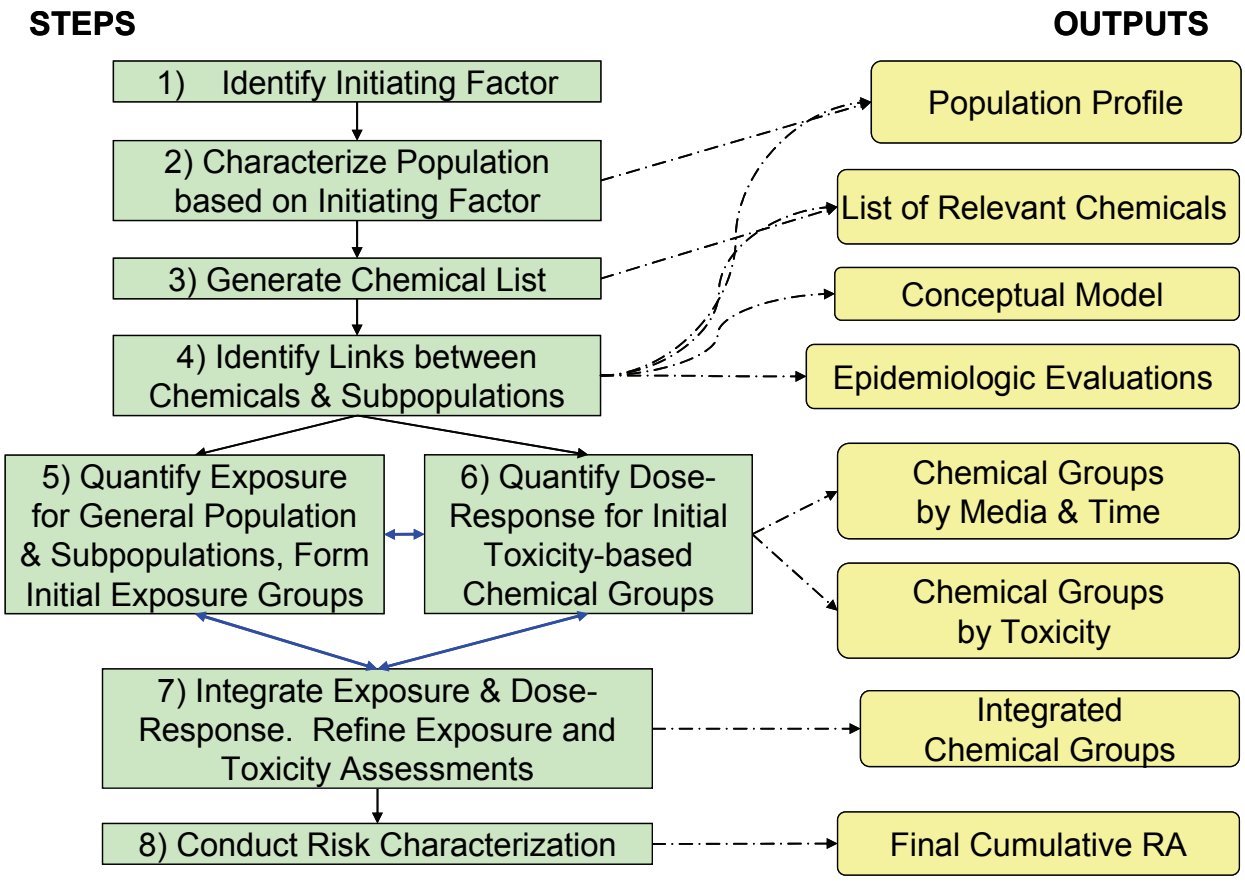


FIGURE ES-5

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

interactions[2]. In addition to providing information about multiple chemical exposures in the general population, these exposure assessments identify potentially susceptible or vulnerable subpopulations[3] in the study area and potentially unique pathways of exposure in those subpopulations.

Cumulative exposure assessments will likely rely on environmental monitoring data and environmental fate models. The community's boundary may define the geographic region of study for a cumulative exposure assessment, unlike chemical-focused assessments or single source-focused assessments. If the timing of different chemical exposures is important, the analyst can use fate models 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 either close to or distant from the population of concern. The environmental fate information for such an assessment could be site dependent.

While approaches to exposure assessment modeling are stressed in this chapter, the use of biomonitoring data (e.g., biomarkers of exposure) holds a great deal of promise for future cumulative risk assessments. The use of biomarkers in cumulative risk assessments currently is limited. They can provide key quantitative exposure estimates in cumulative risk assessments (e.g., biomarker data are used to estimate current chemical exposure levels in an affected population or the general population). Such data also can be used to verify selected exposure model results (e.g., show that specific chemical exposures and absorption are occurring in the population or, if the data are collected in a different location or under different conditions, provide evidence showing that human absorption of the chemical from environmental exposures are possible). For example, some studies have used existing blood chemical or urine chemical concentration data, such as data published in NHANES (NCHS, 2002).

Exclusive use of biomarker data in cumulative exposure assessment efforts is currently not practicable when considering a large number of diverse chemicals due to analytical and resource limitations. Analytical limitations include considerations such as whether sensitive biomarkers for many types of environmental chemicals have been

[2] Toxicodynamic interactions encompass all interactions that do not directly affect absorption, distribution, metabolism or elimination of a toxic chemical. Toxicodynamic interactions affect a tissue's response or susceptibility to chemically mediated toxic injury. Modes of toxicodynamic interactions include, among others, depletion or induction of protective factors, alterations in tissue repair, changes in hemodynamics, and immunomodulation. See Appendix C U.S. EPA (2000a) for complete discussion.

[3] Vulnerable or susceptible populations in the study area can be identified during either the exposure or dose-response assessment phases of a cumulative risk assessment. This identification is based on properties of the chemicals being evaluated as well as social, cultural or genetic factors that influence vulnerability or susceptibility.

developed and whether the chemical's biological half-life after absorption is sufficient to estimate exposure over a relevant exposure period. Collection of human biomarker data can be invasive and costly, resource limitations may constrain the ability of researchers to collect such data.

If collected, the interpretation of biomonitoring data and application to risk assessment can be challenging. While biomonitoring identifies individuals who are exposed and have measured internal doses reflecting absorption of a chemical, to estimate the individuals' actual exposures, the biomonitoring data would need to be integrated with additional information (e.g., exposure modeling information) to identify the pathways, timing and routes of exposure. Additional exposure and environmental modeling would be needed to identify sources of chemicals in the contaminated media. Although the use of biomonitoring data holds great promise for cumulative risk assessments, few methods exist at this time for such applications (U.S. EPA, 2003a).

Exposure models may be divided two general categories: screening and refined. Screening models involve relatively simple estimation techniques and generally use preset, worst-case conditions to produce conservative estimates of the environmental quality impact of a specific source or source category. Analysts use these instead of more detailed (and more expensive) models to assess sources that clearly will not cause or contribute to ambient concentrations above established standards for public health. 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 the analysts would apply refined models for a more representative assessment.

An example of a refined approach for detailed consideration of exposure timing in dose/response assessment is the EPA's Office of Pesticide Policy approach, identified as the *calendar approach*, in *General Principles for Performing Aggregate Exposure and Risk Assessments* (U.S. EPA, 2001a). 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 pesticides in the spring and summer) with routine exposures (e.g., contaminants in the food supply).

Mixtures occurring in a community may originate from different sources. Thus, information about sources of chemical pollutants, chemical properties and fate can be organized to guide chemical groupings that reflect the coexistence in media to which people can be exposed within contaminated communities. The grouping of the chemicals could be based on the potential for their co-occurrence in each

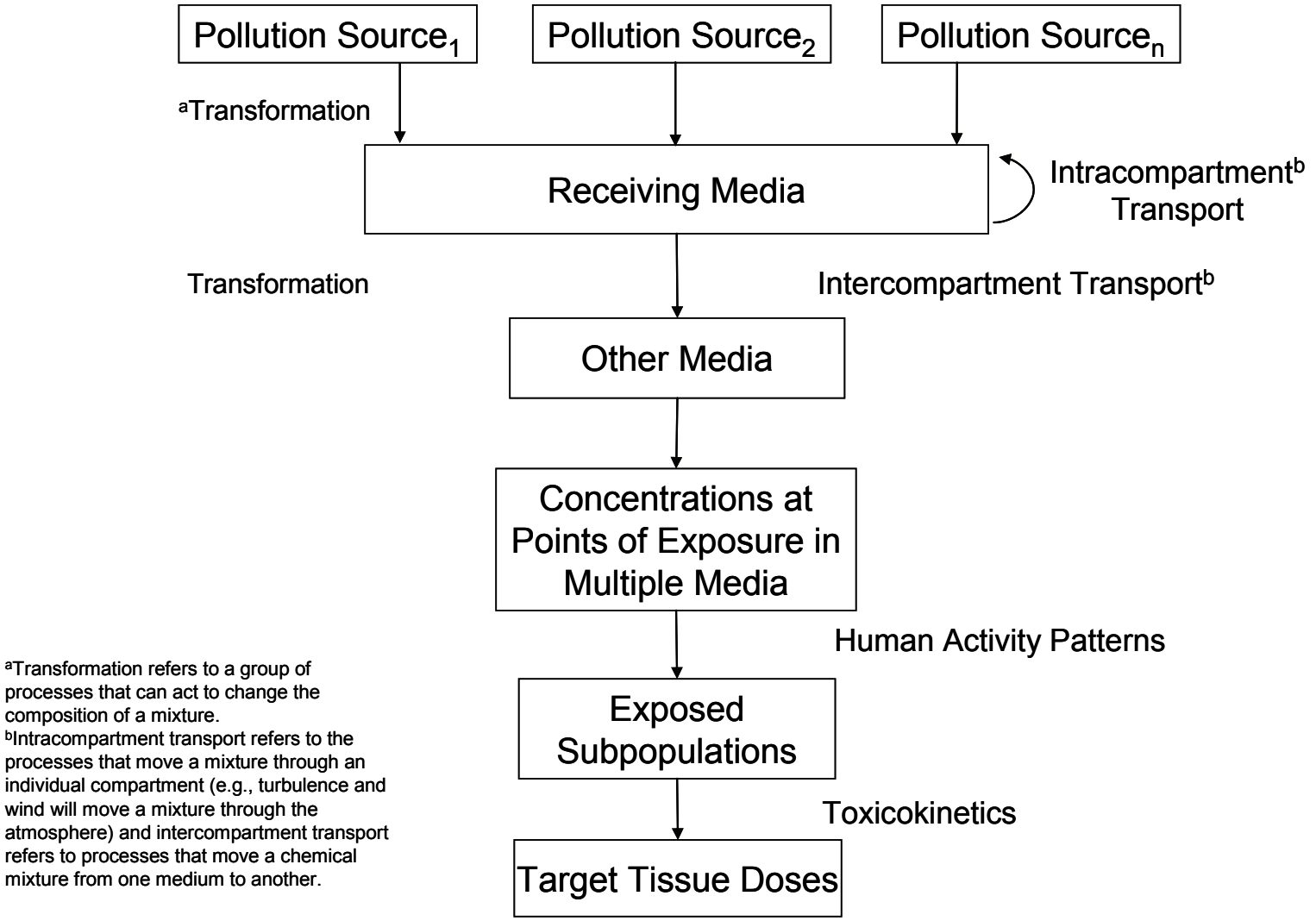
compartment/medium, potential for interactions affecting transformation and potential for co-occurrence and interaction along each transport pathway between media. Figure ES-6 provides an overview of how this information might be organized according to media and the processes of fate and transport.

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 expected to control initial contamination and migration behavior in the environment. 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.

Groups of chemicals may be expected to be distributed to various environmental compartments (or media). An implicit assumption is 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 process 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 some cumulative risk assessments, it may be important to examine when these chemical movements would occur.

This concept is illustrated for an example release scenario (industrial spill) in Table ES-1. This concept applies to any environmental release, so other scenarios can also be considered, such as combustor emissions related to routine operations or temporary releases (e.g., due to excursions from a continuous-operation facility or discrete releases from a mobile facility). The result is an initial set of chemical groups that can be further refined in the toxicity assessment and then used for Risk Characterization and uncertainty analysis.

Text Box ES-1 summarizes a general comparison of the processes involved in conducting a basic versus a cumulative exposure assessment. 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.



[a]Transformation refers to a group of processes that can act to change the composition of a mixture.
[b]Intracompartment transport refers to the processes that move a mixture through an individual compartment (e.g., turbulence and wind will move a mixture through the atmosphere) and intercompartment transport refers to processes that move a chemical mixture from one medium to another.

FIGURE ES-6
Approach for Estimating Exposure in Cumulative Risk Assessments

TABLE ES-1

Example Groupings Based on Exposure Considerations (Media and Timing)*

	Release Scenario		
	Industrial Spill on Soil near a River (VOCs, SVOCs and Metals)		
Exposure	Acute to Short-Term		Long-Term
Duration	<Day to weeks	Months	Years
Environmental Medium - Transport/ Removal Process	Chemicals Projected to Be in Various Media over Time		
Soil upper horizon - volatilization and leaching from surface, biodegradation	CCl_4, DCA, DCE, TCE, VC; PCBs; As, Cd, Cr, Hg, Ni	PCBs; As, Cd, Cr, Hg, Ni	(possibly PCBs) As, Cd, Cr, Hg, Ni
Air - volatilization from soil	CCl_4, DCA, DCE, TCE, VC; PCBs	CCl_4; PCBs	(possibly PCBs)
Surface water (river) - overland flow and particle transport from surface soil	CCl_4, DCA, DCE, TCE, VC; PCBs; As, Cd, Cr, Hg, Ni	CCl_4, DCE, TCE; PCBs; As, Cd, Cr, Hg, Ni	(possibly PCBs)
Aquatic sediments - precipitation from water, adsorption on particles, deposition	CCl_4, DCE, TCE, VC; PCBs; As, Cd, Cr, Hg, Ni	CCl_4, TCE, VC; PCBs; As, Cd, Cr, Hg, Ni	PCBs; As, Cd, Cr, Hg, Ni
Soil lower horizons - leaching from surface soil, adsorption and biodegradation	CCl_4, DCA, DCE, TCE, VC; PCBs; As, Cd, Cr, Hg, Ni	CCl_4, TCE, VC; PCBs; As, Cd, Cr, Hg, Ni	PCBs; As, Cd, Cr, Hg, Ni
Groundwater - leaching from soil		CCl_4, DCA, DCE, TCE, VC	CCl_4, DCA, DCE, TCE, VC; PCBs; As, Cd, Cr, Hg, Ni

* Projected intervals reflect physical-chemical properties and fate data, including half-lives; other factors also affect partitioning and timing, including local conditions such as temperature (for volatilization); organic content (for soil and sediment sorption), which for this example is assumed to be relatively low; and depth to aquifer (for leaching to groundwater), which is assumed to be moderate to deep.
As = arsenic; CCl_4 = carbon tetrachloride; Cd = cadmium; Cr = chromium; DCA = 1,1-dichloroethane; DCE = 1,1-dichloroethylene; Hg = mercury; Ni = nickel; PCBs = polychlorinated biphenyls; SVOCs = semivolatile organic compounds; TCE = trichloroethylene; VC = vinyl chloride; VOCs = volatile organic compounds.

Comparison of Exposure Assessment Processes *(Text Box ES-1)*

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

ES.5. TOXICITY ASSESSMENT OF MULTIPLE CHEMICALS, EXPOSURES AND EFFECTS

Assessments of adverse health effects from exposures to multiple chemicals through multiple routes of exposure over time may account for multiple health effects and for joint toxic action resulting from exposure to a chemical mixture. Risk assessments may include evaluation of the timing and intensity of exposures to different chemicals, including the examination of internal co-occurrence of multiple chemicals and toxicological interactions in the target tissue(s). Cumulative risk assessments add layers of complexity to the evaluation of chemical mixtures. Methods for cumulative risk assessment may be developed by expanding on the theory and methods presented in the EPA's *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 2000a) to evaluate various aspects of cumulative risk. Figures ES-7a and ES-7b present both established methods along with new or enhanced methods for cumulative risk assessment. For example, Figure ES-7a shows the development of toxicity values (i.e., Reference Doses [RfDs], Reference Concentrations [RfCs] and slope factors) as presented in the 2000 *Supplementary Mixtures Guidance* for whole mixtures and sufficiently similar mixtures, but Figure ES-7a also includes additional epidemiologic evaluations that may be useful when illnesses in

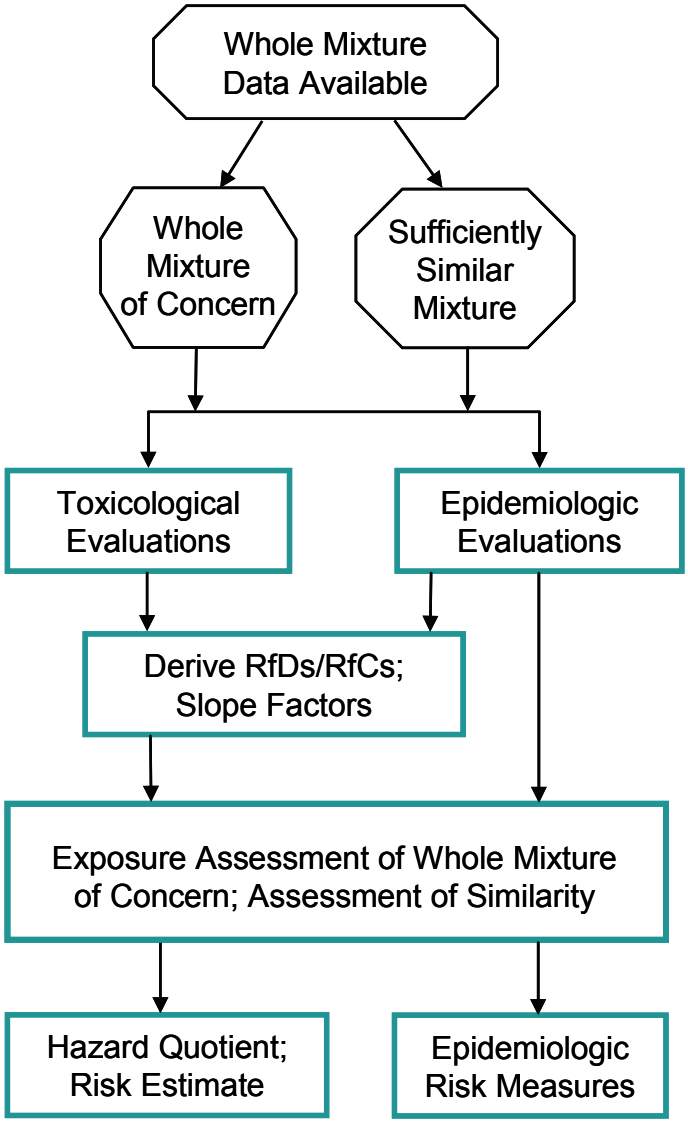
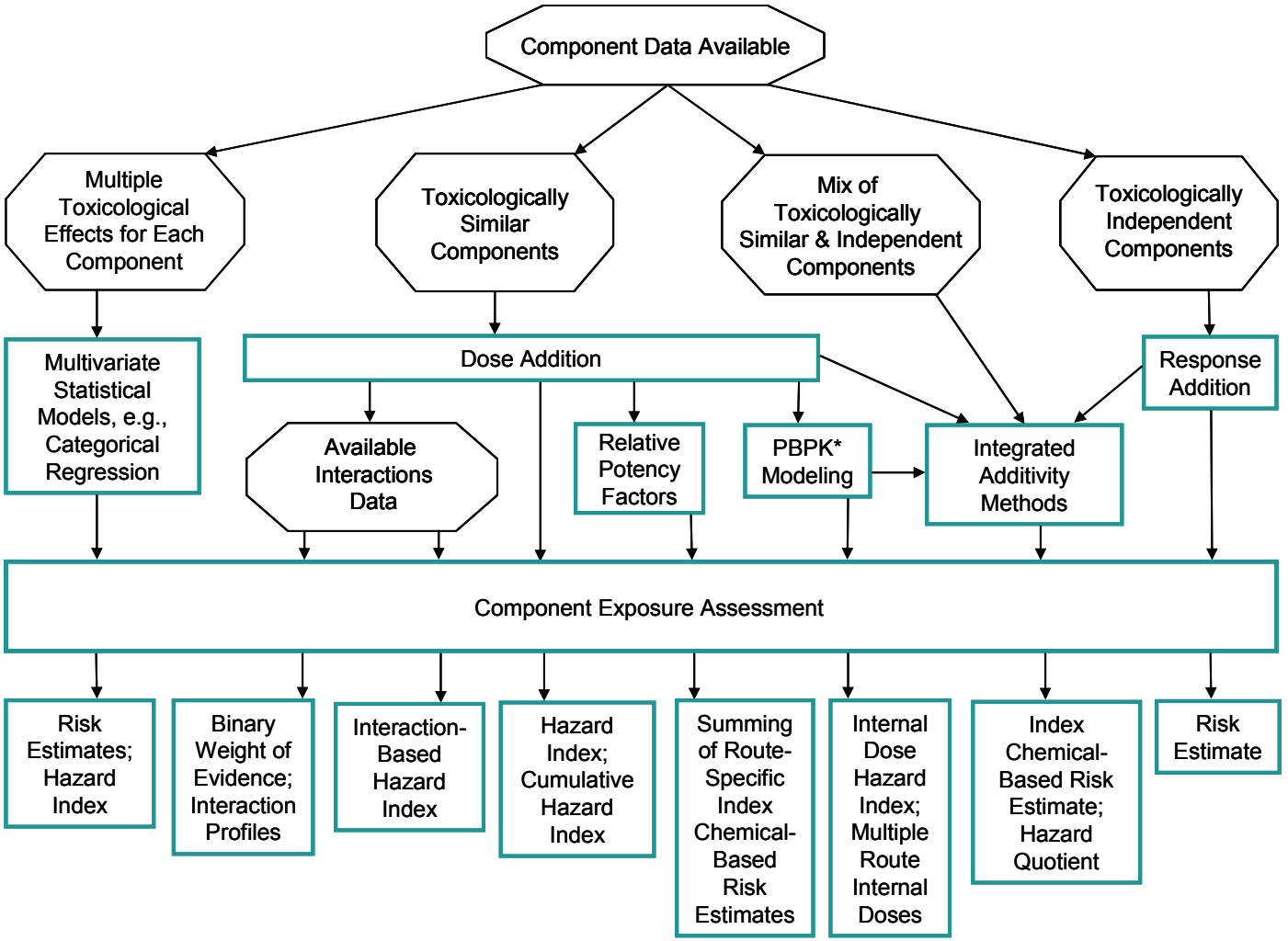


FIGURE ES-7a
Flow Chart Showing Approaches for Evaluating Whole Mixtures



*PBPK = physiologically-based pharmacokinetic

FIGURE ES-7b

Flow Chart Showing the Component Based Approaches for Evaluating Multiple Chemicals, Exposure Routes, Effects and Toxicological Interactions

the population initiates a cumulative risk assessment. Figure ES-7b presents established component-based chemical mixtures methods (i.e., RPFs, HI, Response Addition and the Interaction-Based HI), but several other approaches for use in cumulative risk assessment are also reflected in this figure. Further, Figure ES-7b handles not only toxicologically similar and dissimilar mixtures, but also addresses mixes of these, as well as addressing the case of multiple toxicological effects. Finally, additional methods are shown that include the use of PBPK models to estimate internal doses of chemicals and examine the potential for toxicological interactions.

Grouping chemicals by the potential for co-occurrence and joint toxic action is a key simplifying concept in this report. Chemical components of mixtures can be screened for inclusion in a cumulative risk assessment using the elements of component-based methods. Figures ES-8a, ES-8b and ES-8c outline a process for classifying chemicals into groups suitable for analysis and the application of the methods shown in Figures ES-7a and ES-7b. This process includes the following steps:

1) Figure ES-8a—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.
2) Figure ES-8a—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 is to collect toxicological 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 ES-8b and ES-8c—Assess the toxic potential of the chemicals and whole mixtures of concern using methods shown in Figures ES-7a and ES-7b. Figure ES-8b shows a flow chart that first evaluates the whole mixtures and single chemicals for toxicity potential, ensuring that those with the greatest potential to cause toxicity are maintained in the cumulative risk assessment. Then, the chemical groups formed in Figure ES-8a are evaluated for joint toxicity, addressing multiple effects, interactions and exposure routes; these groups are then screened into or out of the cumulative risk assessment. Figure ES-8c provides additional detail on the processes shown in Figure ES-8b, indicating the methods and outputs from this data analysis.

The methods developed for cumulative toxicity assessment may be used in several different ways depending on data availability and on the goals of the assessment. They may be applied as screening tools (e.g., to decide whether or not toxicological interactions are of importance for a certain group of chemicals) or as tools

	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
Chemicals in Exposure Groups (Above) Further Grouped Based on Similar Toxicity				
Kidney	Hg, Cd, BDCM	Ni, TCE, U, Cr	Hg, BDCM	Cd, TCE, Ni, Cr
Brain	Hg, DCA	TCE, As, Ni, CCl_4	Hg, DCA, PCB	TCE, As, Ni, CCl_4
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 ES-8a

Hypothetical Example of Chemical Groupings by Co-occurrence in Media and Time, Similar Toxicity

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

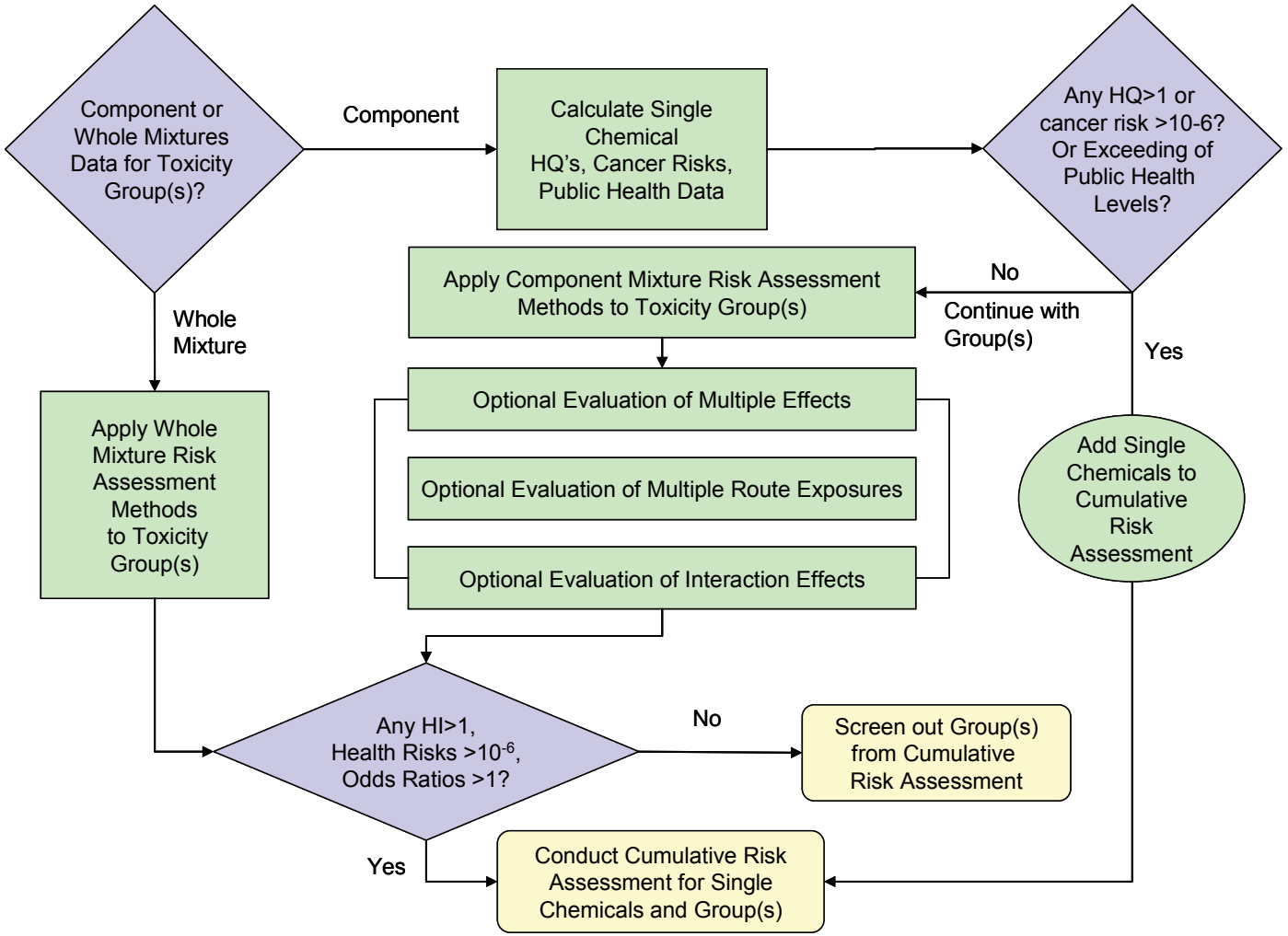


FIGURE ES-8b

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.

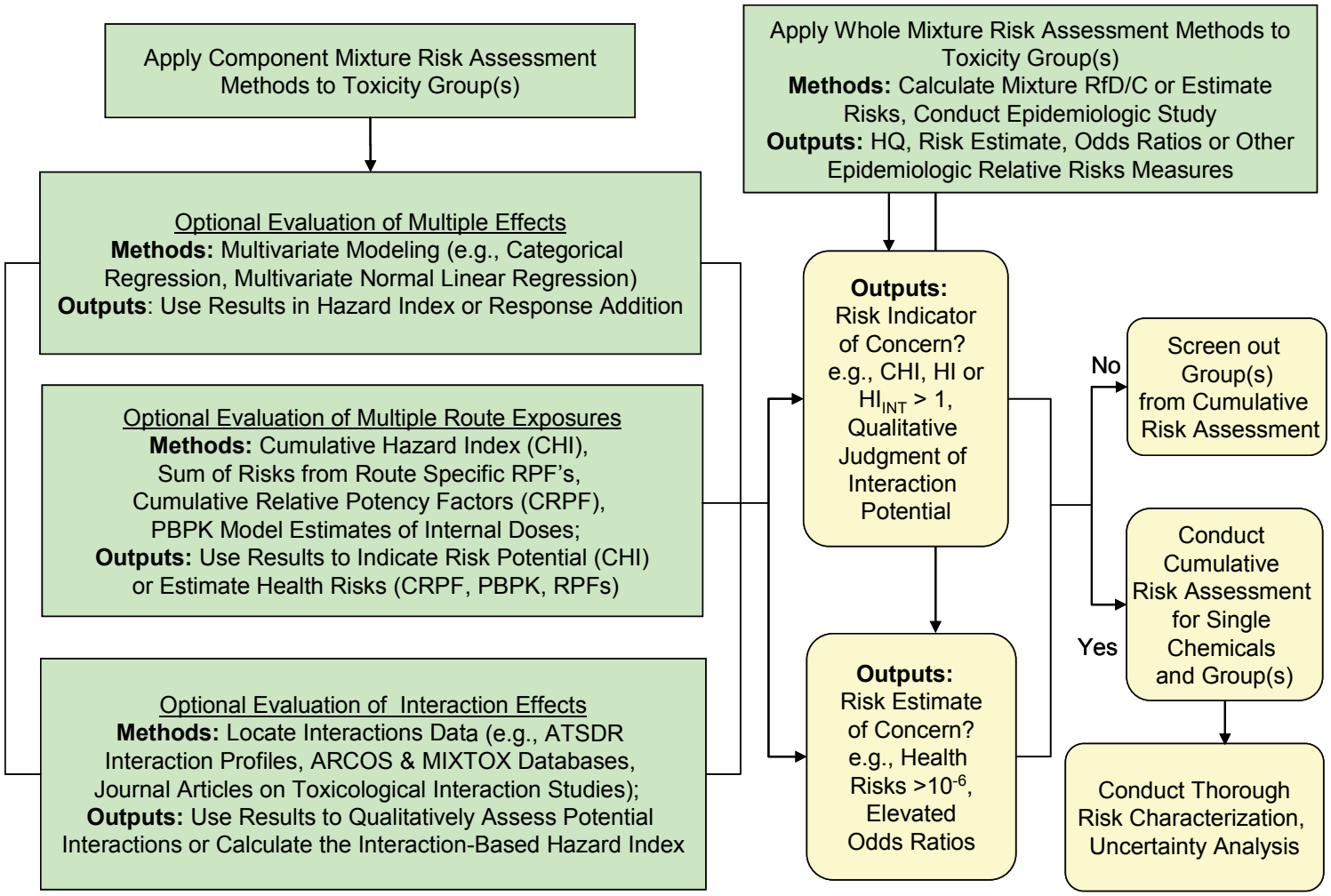


FIGURE ES-8c

Grouping Chemicals for Cumulative Risk Assessment (cont). Specific mixture risk methods are applied depending on which multiples are being evaluated, with "concern" judged by the appropriate screening value as determined during the Problem Formulation stage of CRA.

for estimating quantitative risk numbers (e.g., estimating the risk of an adverse level of cholinesterase inhibition by applying a RPF approach to a group of pesticides). In some cases all of the methods shown might be applied, and in other cases, only a select few methods would be useful depending on the exposure scenario.

ES.6. RISK CHARACTERIZATION

A Risk Characterization is usually described as having two parts: an integrative analysis, which contains the risk estimates and can be highly technical, and a risk characterization summary, which focuses on recommendations and uncertainties. Figure ES-9 provides an overview of the final Risk Characterization process for a cumulative risk assessment. It is an expansion of the final Risk Characterization step shown in Figure ES-5, beginning with outputs from the steps shown in Figure ES-5, such as, the population profile and the integrated chemical groups. The cumulative Risk Characterization may differ from a traditional Risk Characterization in several ways 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 listed below:

- Recommendations could be multivariate (i.e., it may be difficult to identify a single chemical, pathway or critical effect that drives the risk)
- Recommendations might be based on groupings of chemicals, pathways and effects, but such groupings can be based on subjective judgments
- Recommendations might be based on epidemiological findings relevant to a population illness, for which it is useful to articulate confounding factors and exposure uncertainties
- Uncertainty analysis might be predominantly qualitative because of the use of numerous defaults (e.g., for addressing interactions and multiple effects).

In summary, in the Risk Characterization phase of cumulative risk assessment, it may be useful to consider issues in the context of evaluating multiple chemicals, exposures and effects, including interaction effects, with respect to the population characteristics. Issues regarding uncertainty, variability and sensitivity analysis are important to present. An integrative technical analysis of the predicted risks is useful, as well as a summary of the results and uncertainties of the Risk Analysis. Risk Characterization results may be used by risk managers in the final Decision-Making stage of a cumulative risk assessment; thus the Planning and Scoping process, data sources, analytical techniques, logic used to make various technical decisions and uncertainty analysis are more useful if they are scientifically sound and presented in a transparent manner.

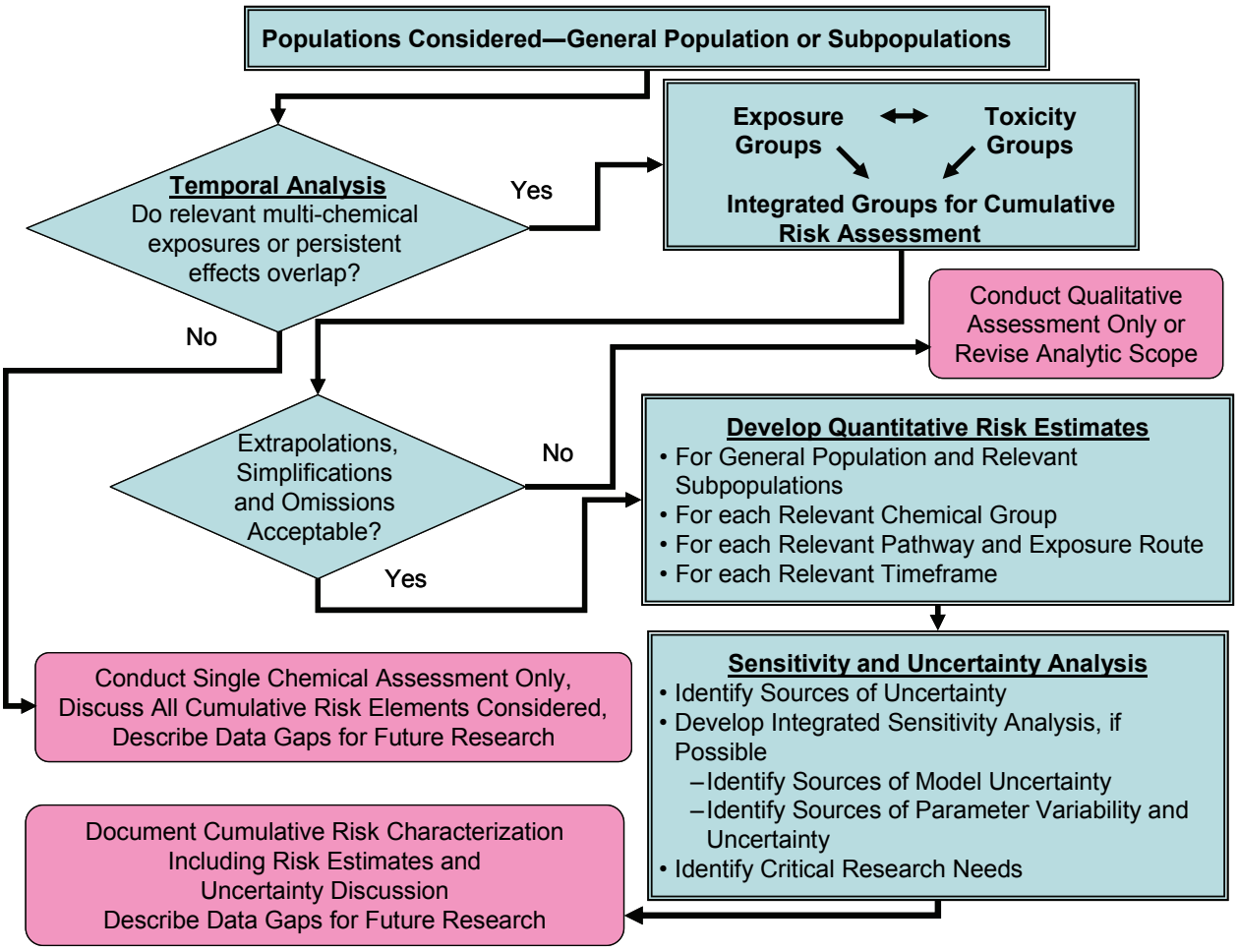


FIGURE ES-9

Schematic of Cumulative Risk Characterization Approach in this Report

1. CUMULATIVE RISK ASSESSMENT INTRODUCTION

1.1. BACKGROUND

Public interest in and awareness of the health impacts of environmental chemical exposures and their interactions with other stressors continues to grow as more information is assembled about exposures to multiple chemicals in air, water and soil from different sources. In the United States, organizations such as the United States Environmental Protection Agency (EPA) and Agency for Toxic Substances and Disease Registry (ATSDR) have developed documents that support the development of cumulative risk assessment (see ATSDR, 2002c; U.S. EPA, 1997a, 2000a, 2002a, 2003a). Internationally, organizations such as the World Health Organization's International Programme on Chemical Safety, the European Food Safety Authority and NoMiracle (Novel Methods for Integrated Risk Assessment of Cumulative Stressors in Europe) are sponsoring workshops and authoring publications to help increase knowledge on the transfer of pollutants between different environmental compartments, on food safety, and on the impact of cumulative stressors, including chemical mixtures (EFSA, 2006; IPCS, 2006; NoMiracle, 2006).

EPA has responded to increasing requests for ways 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 provide information that organizes and helps explain the scope of cumulative risk assessment. The EPA's *Framework for Cumulative Risk Assessment* (herein referred to as the *Framework* in this report) defines the general concepts and considerations for these assessments (U.S. EPA, 2003a), and earlier reports laid a broad foundation for the initial Planning and Scoping phase needed to conduct a cumulative risk assessment (U.S. EPA, 1997a, 2002a). This current report serves as a resource document for identifying specific elements of and approaches for implementing cumulative risk assessments. This report is not a regulatory document and is not guidance but rather a presentation of concepts, methods and data sources. It is designed to assist EPA's development of specific approaches and cumulative risk guidance for use by its Program Offices and Regions. It is intended as a resource for EPA scientists and others in the broader risk assessment community with an interest in locating data and approaches relevant to cumulative risk assessment.

1.1.1. The Integrated Process for Cumulative Risk Assessment. The *Framework* defines cumulative risk as the combined risks from aggregate exposures (i.e., multiple

route exposures) to multiple agents or stressors, where agents or stressors may include chemicals, as well as biological or physical agents (e.g., noise, nutritional status), or the absence of a necessity such as habitat. Cumulative risk assessment, then, is an analysis, characterization and possible quantification of the combined risks to health or the environment from multiple agents or stressors. Other important aspects of cumulative risk assessment include a population focus, emphasis on stakeholder involvement, consideration of population vulnerabilities, and a focus on both human health and ecology. Areas of vulnerability articulated in the *Framework* for human and biological ecosystems, communities, and populations include susceptibility or sensitivity, differential exposure (e.g., caused by cultural practices or by living in close proximity to pollutant sources), differential preparedness (e.g., lack of disease immunizations), and differential ability to recover. Note that the conduct of a cumulative risk assessment will not be appropriate to every investigation; it is most useful when addressing the risks from multiple stressors acting together (U.S. EPA, 2003a).

The National Research Council (NRC) 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, called the Risk Assessment Paradigm: hazard identification, dose-response assessment, exposure assessment and risk characterization, as explained in Text Box 1-1. These general steps provide the original foundation for risk-based programs across many federal agencies and are an integral part of cumulative risk assessment. The *Framework* incorporates the risk assessment paradigm within the three phases of a cumulative risk assessment that it identifies (see Figure 1-1): (1) Problem Formulation, (2) Risk Analysis and (3) Risk Characterization. Planning and Scoping, an iterative dialogue between the scientists, risk managers and stakeholders, takes place mostly during the Problem Formulation phase but may be revisited as needed during the Risk Analysis and Risk Characterization phases. The output from Risk Characterization is then used to support environmental Decision-Making. Other factors, such as economic, social and policy considerations, may enter into both the Planning and Scoping and the Decision-Making stages of the cumulative risk process. These may influence the design of the analysis or the final risk management decisions.

Summary of Traditional Risk Assessment Paradigm
(Text Box 1-1)

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, how frequently
Dose-response assessment	Quantify dose-response relations and define toxicity values from scientific studies
Risk characterization	Describe cancer risks, noncancer effects and related uncertainties

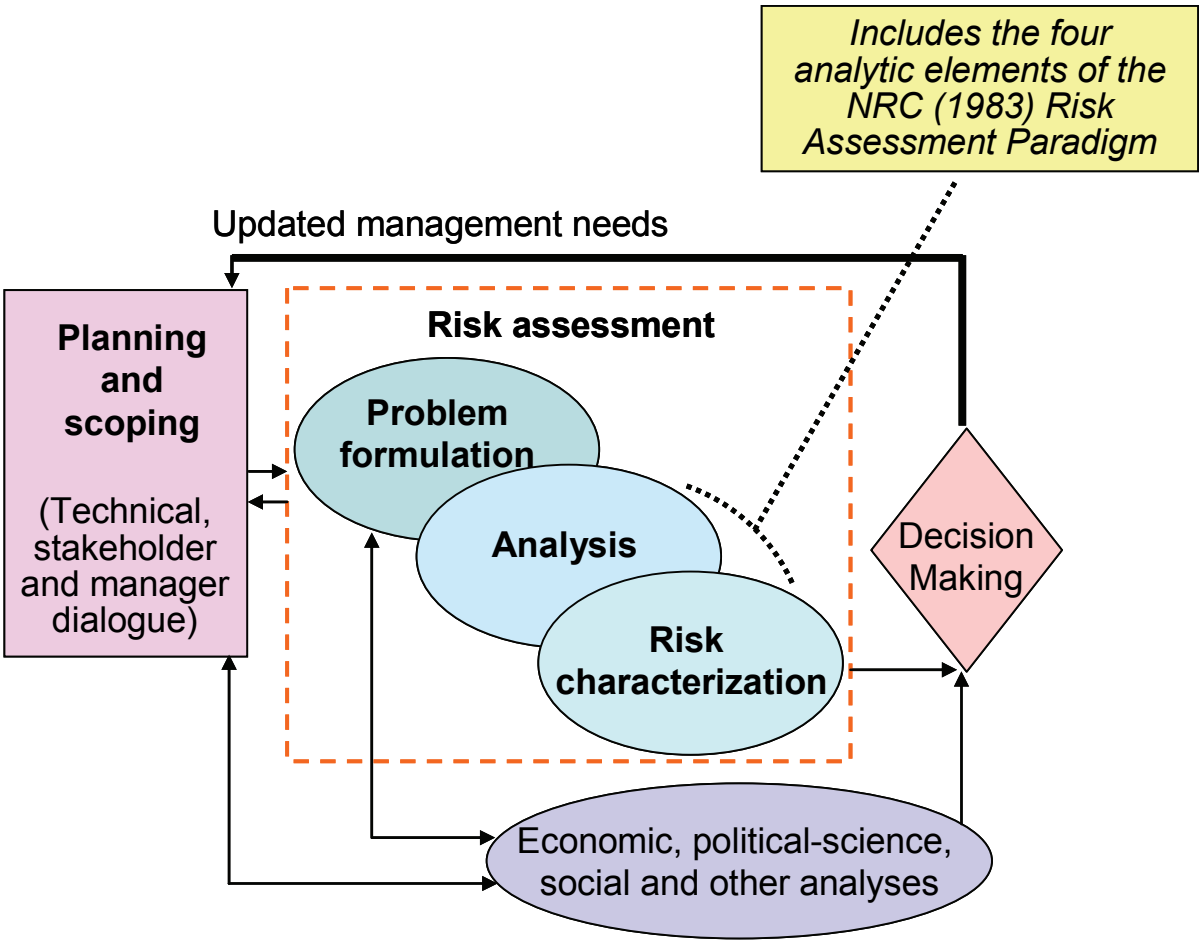


FIGURE 1-1

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

During the Problem Formulation phase, the risk analysts, risk managers and other stakeholders jointly establish the goals, breadth, depth and focus of the assessment, producing a conceptual model and an analysis plan. The conceptual model identifies the stressors to be evaluated and the health or environmental effects to be evaluated; it also describes the possible relationships among various stressors 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 of the *Framework* includes the determination of the analytical and quantitative methods to be used for exposure assessment, dose-response assessment and risk estimation. The exposure and dose-response processes for cumulative risk are expected to occur iteratively to ensure information compatibility. This phase also includes the initial estimates of joint health risk from the multiple stressors to which the study population and sensitive population subgroups are exposed (U.S. EPA, 2003a, p. xviii).

The final phase of a cumulative risk assessment, Risk Characterization, involves further analysis so that the risk estimates are explained in terms of their significance and uncertainties. This is also where the risk assessment process is evaluated to determine whether the objectives and goals of the first phase (Planning and Scoping and Problem Formulation) have been met.

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

Aggregate exposure	Combined exposure to one chemical; can be from multiple sources or pathways
Cumulative risk	Combined risk from exposures to multiple chemicals or stressors; 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 includes (1) source and 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)

1.1.2. Terminology.

Terminology often used for cumulative risk assessment overlaps with terms used in environmental science, chemical mixtures risk assessment and public health. Some common terms are defined in Text Box 1-2. The

glossary (Chapter 7) provides detailed definitions for these and other terms in this report.

For EPA, cumulative risk assessment involves combined risks from multiple exposures to multiple *stressors* from all contributing sources. This assessment addresses a given *receptor population*, whether this is an actual community or a hypothetical population of future inhabitants of a geographic region. 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.

A cumulative risk assessment can involve multiple *exposure pathways* and *exposure routes* that reflect different ways contaminants can enter the body from different media (e.g., breathing air and drinking water). An *exposure pathway* describes how chemicals are transported from a source to a person or subpopulation (e.g., through the air or water). An *exposure route* identifies the way the contaminant actually enters the body.

These assessments also consider multiple *effects* within two main categories: cancer and noncarcinogenic systemic effects. For the latter, in a cumulative risk assessment involving multiple chemicals, it is important to include an evaluation of both critical and secondary 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 effects are typically those seen at higher doses in the same target organ or tissue and/or different physiological compartment(s) and are rarely incorporated into a single chemical risk assessment beyond uncertainty analysis of the entire relevant toxicity database. In the assessment of chemical mixtures, an important difference from single chemical assessments is that the health effects observed as a result of combined chemical exposures may differ in phenotype and/or magnitude from the critical effects caused by the individual chemical exposures. Thus, it is important to evaluate secondary effects for those chemicals to which humans may be exposed in combination. In these cases, the doses of the chemicals in the mixture may act in an additive manner to cause one of these secondary or higher level effects, or the responses (effects or risks) themselves may be additive. In addition, co-exposure to multiple chemicals may result in toxicological interactions (e.g., synergism or antagonism) that lead to secondary or higher level effects. Thus, in a cumulative risk

assessment involving more than one chemical as a stressor, it is important to consider evaluating critical effects as well as secondary and higher level effects.

Multiple stressors are central to cumulative risk analyses. Multiple stressors include vulnerability factors and chemical, physical and biological exposures. The EPA defines as an *aggregate exposure assessment* as an assessment that seeks to characterize a single-chemical exposure that could involve multiple exposure pathways (be present in many sources or media) and potentially taken in by multiple routes (oral, dermal, etc.). 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 of this report. In the environment, interactions can alter the fate and transport of 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 defined as 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 EPA has defined the specific term, *toxicological interactions*, to represent interactions that are other than additive (U.S. EPA, 2000a). The EPA has developed an interaction formula based on departures from dose addition (see Chapter 4). Toxicological interactions are then commonly defined by 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 reported synergistic effect of cadmium (Cd) and lead (Pb) on the neurological system or the reported antagonistic effect of Cd and Pb on the kidney (see Chapters 4 and 5). Such interactions are a common concern at contaminated sites.

1.2. ABOUT THIS REPORT

As discussed above, cumulative risk assessment covers a breadth of topics which may include combination toxicology, chemical mixtures, multiple exposure pathways and exposure durations, and can extend from identifying how the assessment was initiated to determining how the analysis will be conducted and how results will be presented. Building on the concepts that have been identified in earlier reports and offering examples to illustrate how those concepts can be applied, this report addresses only human health assessment (as shown in Figure 1-2), and focuses on two areas: (1) concepts concerning the initiating factors for a cumulative risk assessment with procedures for data collection and organization (Chapters 1 and 2) and (2) technical

approaches for assessing and characterizing health risks associated with a subset of cumulative risk issues (i.e., multiple chemicals, exposures and effects), with examples pertaining to contaminated sites, drinking water and ambient air (Chapters 3, 4 and 5). The report's organization is as follows:

Chapters 1 and 2 present information on cumulative risk assessment initiating factors, data collection and organization. Both chapters describe elements of the Problem Formulation phase, i.e., the preliminary characterization of the population assessed, the initial identification of the chemicals, exposures and effects of concern and an evaluation of the potential relationship between population illness and chemical exposures. Procedural steps for a cumulative risk assessment are described, and the differences between population-based cumulative risk assessments and traditional source-based or chemical-based risk assessments are highlighted.

Chapter 1 discusses the development of cumulative risk assessment theory and procedures, provides background information and describes the organization and content of the current report. Chapter 1 also presents an overview of cumulative risk processes and a summary of the approach proposed in this report to address cumulative risk, emphasizing the factors that could initiate the decision to undertake a cumulative assessment.

Chapter 2 discusses the initial characterization of the population and identification of relevant chemicals as influenced by the initiating factor that initiated the cumulative risk assessment, It discusses data collection and organization, the use of public health information and epidemiologic approaches, and it ends with a discussion of conceptual models for identifying links between environmental exposures and target populations.

Chapters 3, 4 and 5 present information on technical approaches to the Analysis and Risk Characterization of multiple chemicals, exposures and effects. (Figure 1-2 illustrates this narrow focus on a subset of cumulative risk issues.) These include evaluations of exposures and risks using chemical mixtures methods; approaches for grouping chemicals for Risk Analysis and Risk Characterization; evaluating assumptions and uncertainties; and deciding whether to conduct a qualitative or a quantitative assessment.

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

Chapter 4 explains and illustrates key toxicity concepts and chemical mixture risk assessment methods that may be used to evaluate multiple effects, exposures and toxicological interactions. The chemical groups first established using exposure information are further defined based on

common toxicological action. The influence of exposure information on the toxicity assessment is discussed.

Chapter 5 provides information for the Risk Characterization phase, including a discussion of issues to be addressed, methods for evaluating some of the uncertainties inherent in cumulative risk assessments and the need for comparison of results with the goals from the Planning and Scoping phase.

Supporting Information

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

Chapter 7 defines basic terms used in cumulative risk assessments.

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 risk assessments.

Appendix C presents a discussion on the history and use of toxicological severity concepts in risk assessments.

As shown in Figure 1-2, this report covers only some of the many aspects of cumulative risk for human health assessment (not ecological assessment), so it is important to note the areas that it does not consider. For example, while multiple chemicals and exposures and both cancer and noncancer health endpoints are addressed, approaches for interactions with non-chemical stressors, such as noise, or for other kinds of risks, such as microbial or ecological risks, are not included. The important issues related to stakeholder involvement in Planning and Scoping and risk communication are also not included as they are described in previous documents (U.S. EPA, 1997a, 2002a). In addition, social, political and economic issues are not discussed and only some aspects of vulnerability are highlighted. Finally, this report does not address the final risk management decision or the communication of such a report to interested audiences.

1.2.1. Innovations Included in this Report. Within its targeted scope, this report addresses certain aspects of the Problem Formulation, Risk Analysis and Risk Characterization phases involved in implementing a cumulative risk assessment. In actual applications, some of the approaches shown in this report may be extended more broadly to assess other types of stressors complex exposures and vulnerability issues. Many of the techniques have roots in previous EPA documents, such as the 2000 *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures*

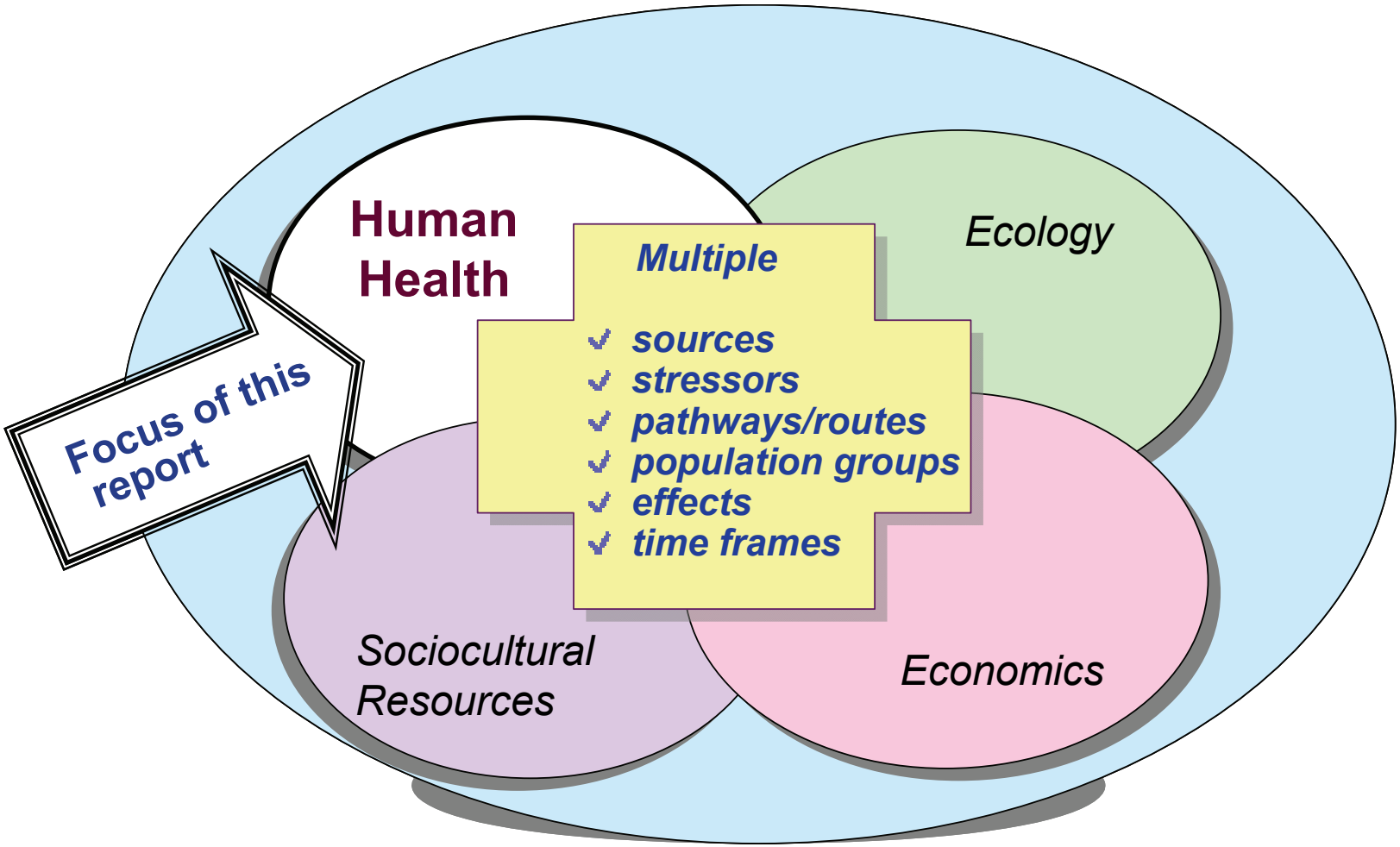


FIGURE 1-2
Assessing Integrated Multiples in Cumulative Risk Assessment: Focus on Human Health

(U.S. EPA, 2000a) (herein referred to as the 2000 *Supplementary Mixtures Guidance* in this report) but new material is also presented with detail on how existing methods can be extended to address areas the 2000 *Supplementary Mixtures Guidance* does not cover (e.g., multiple route exposures to multiple chemicals and effects). This report also brings information together from various sources to show how existing methods and data can be used (see the toolbox in Appendix A). Innovations in methodology include the following:

- developing a description of initiating factors for a Cumulative Risk Assessment and procedures for population characterization, data collection and organization based on the initiating factors (Chapters 1 and 2);
- implementing *chemical grouping*, a potentially helpful way to scope analyses into manageable pieces to be assessed as chemical mixtures with co-occurring exposures (Chapters 3 and 4);
- approaches and data sources for evaluating the timing of exposures, including discussions of kinetics and dynamics (Chapters 3 and 4);
- integrating internal dose measurements to account for multiple route exposures (Chapters 3 and 4);
- further developing the quantitative method for the interaction-based hazard index (HI), first introduced in the 2000 mixtures guidance document (U.S. EPA, 2000a) (Chapter 4);
- extending the Relative Potency Factors (RFP) method to cumulate across exposure routes, an approach expanded an earlier EPA report on drinking water DBP mixtures (U.S. EPA, 2000e) (Chapter 4);
- integrating output from multiple effects modeling (illustrated using a categorical regression model) with the HI and response addition models to express risks for multiple health effects (Chapter 4);providing added detail on the cumulative HI approach used by the Superfund program (U.S. EPA, 1989a), including discussion of the impacts for risk characterization (Chapters 4 and 5);
- presentation of a method for cumulative risk characterization considers factors unique to conduct of a Cumulative Risk Assessment, including the recognition of uncertainties in cumulative dose-response and exposure assessment (Chapter 5); and
- a general emphasis on integrating exposure and dose-response analysis (Chapters 3, 4 and 5).

1.3. EXISTING EPA PUBLICATIONS RELATED TO CUMULATIVE RISK

This report is linked to, and relies upon, several key guidance documents across EPA, as illustrated by the examples in Figure 1-3. EPA's Office of Research and

Development (ORD) has prepared and coordinated a number of major reports that cover the topics shown in the next paragraph, and other EPA Program Offices have developed issue papers and guidance documents 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 EPA guidance documents and reports that address issues related to risk assessment, such as Data Quality Objectives, but do not explicitly address the issues related to cumulative risk; they are discussed in Appendix A.) Dates shown on that figure are for selected major reports within the program areas; additional publications are described in the balance of this report (e.g. see U.S. EPA, 2001a, 2002a,b, 2003b). Other sections of this report describe publications developed by ATSDR and other organizations that support cumulative risk analyses. The publications shown in Figure 1-4 focus on distinct parts of cumulative risk assessment rather than on all aspects described in the *Framework*. This is because those documents 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 chemical mixtures or Planning and Scoping. Other reports will continue to be developed to address the various steps and issues in the *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 human health risks (but addresses only one type of risk). The 2001 national air toxics assessment of more than 30 priority urban air toxics does not address toxic interactions; however, default chemical mixture methods based on additivity concepts are applied. The 2002 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. The 2000 *Supplementary Mixtures Guidance* does not address aggregate exposures, only multiple chemicals by the same exposure route.

1.3.1. EPA Guidance Documents. The four steps of the risk assessment paradigm (NRC, 1983), hazard identification, exposure assessment, dose-response assessment, and risk characterization, provide the original foundation for risk-based programs across many federal agencies (see Text Box 1-1). They are reflected in most EPA guidance for assessing risks, such as the Risk Assessment Guidance for Superfund (RAGs) (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

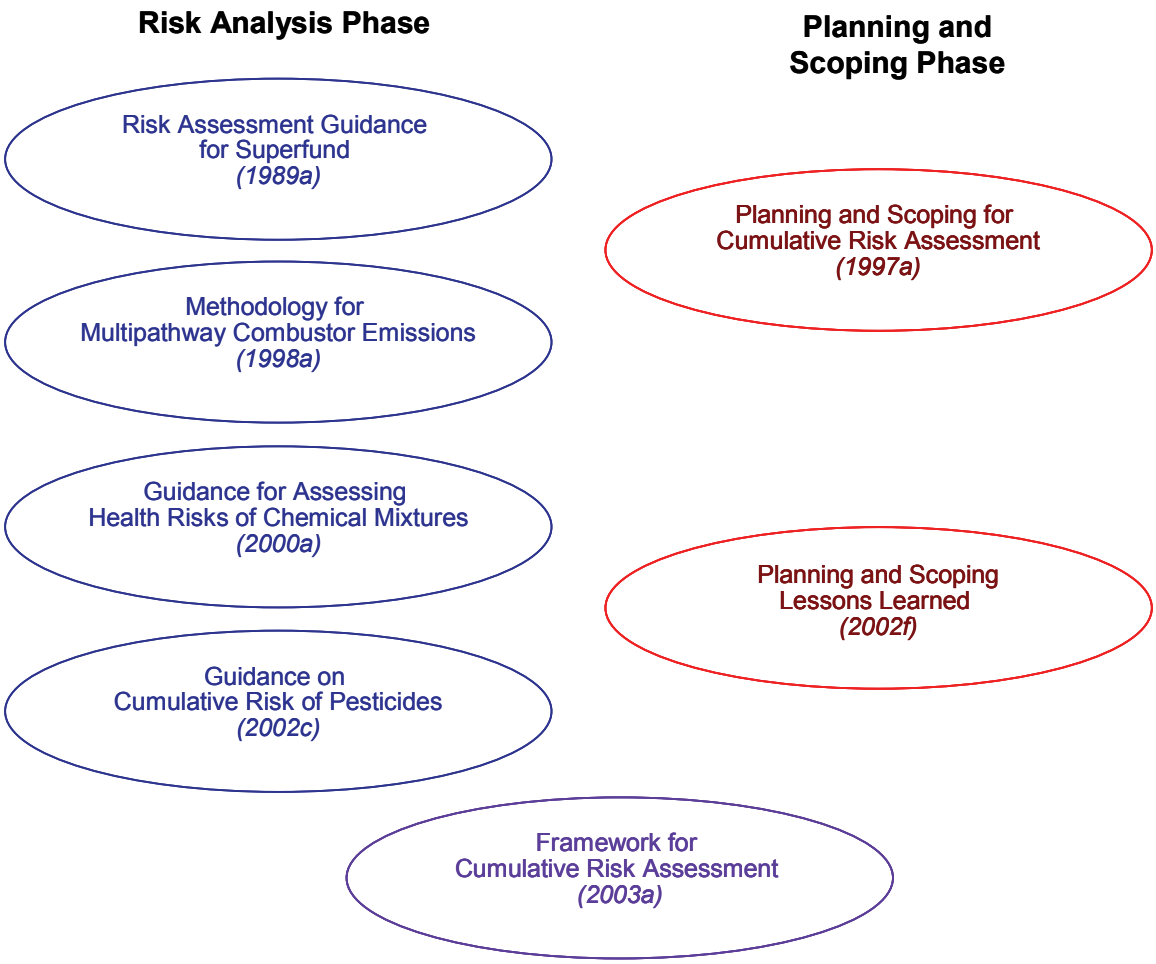


FIGURE 1-3

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

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: 2000a (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: 2002a,c (organophosphates assessment and guidance)

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: 2000e, 2003b (initial risk report, other reports coming)

Multi-pathways Exposures for Combustor Emissions
What: health risks of multi-pathway exposures to combustor emissions
Why: address Clean Air Act requirements
Who: National Center for Environmental Assessment
When: 1998a (methods document)

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: 1997a (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: 2002f (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: 2002b (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: 2003a (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: 2006 (effort underway, no report yet)

Developing 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: 2007 (this report)

FIGURE 1-4
Highlights of Cumulative Risk-Related Program Guidance and Research Reports

air standards, drinking water standards and regulation of pesticides, also are structured roughly along the four steps of the risk assessment paradigm.

In risk-based standard setting (e.g., setting a national safe exposure level for a chemical), 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; in RAGs, 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 RAGs calls for considering multiple chemicals, exposure routes and effects (thus cumulative risks), few specific suggestions are provided that would enable an analyst to extend analysis beyond the basic additive approach in the original EPA mixture guidelines (U.S. EPA, 1986a), primarily because of limitations in current understanding of environmental and toxicological interactions.

As knowledge of the environmental fate and toxicology of chemicals has increased through ongoing research, the risk assessment process has kept pace. The National Research Council has 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 2000 *Supplementary Mixtures Guidance*, the four originally distinct steps of the risk assessment paradigm are now closely linked; in particular, it is useful to jointly conduct the exposure and toxicity evaluations so that the exposure assessment can be refined based on toxicity information and vice versa. During the past several years the EPA has published several cumulative risk documents (as illustrated in Figure 1-4) that capture this shift and extend assessment concepts beyond the original basic approach.

For example, the 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 *Framework* document defines a flexible structure that includes Planning and 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 EPA publications 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 EPA publications 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 encompass all sources, stressors, exposures, affected population groups and effects can be better understood and ultimately better assessed. 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 in, metabolized by and distributed in or eliminated from the body; and whether their combined toxicity could differ from that estimated from the single chemical toxicities. This report illustrates how this new information can be applied to better address cumulative health risks. Sections 1.5.1-1.5.3 provide detail on three existing 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 cumulative risk areas not addressed in those documents.

1.3.1.1. Mixtures Risk Assessment—A common application of mixture risk assessment methods is 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 EPA mixtures guidelines (U.S. EPA, 1986a), 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 toxicological understanding and quantitative data on interactions were limited. To help address this issue, the EPA released the 2000 *Supplementary Mixtures Guidance*, which updates the earlier guidelines by providing further methodologic 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, toxicological similarity based on varying evidence (from similar toxic mechanisms to similar target organs) and toxicological interactions.

A main issue not addressed in the 2000 *Supplementary Mixtures Guidance* is approaches for assessing multipathway exposures to chemical mixtures as well as approaches for multiple effects from chemical mixture exposures.

1.3.1.2. Superfund Site Assessment—RAGs, the standard guidance for assessing health risks at Superfund sites, (U.S. EPA, 1989a) and subsequent companion documents require the consideration of multiple chemicals, sources, exposure routes, receptors and effects. Thus, a basic cumulative assessment is already being conducted at Superfund sites. As mentioned previously, RAGs does not explain how to assess toxic interactions because quantitative methods were limited when it was published. Instead, a default approach was defined under which chemicals are evaluated individually, and doses and toxic responses were assumed to be additive, providing the first 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 form the familiar HI (see Chapter 4). RAGs also developed the quantitative evaluation of multiple pathway exposures with the total Hazard Quotient (HQ) concept (see Chapters 4 and 5). Because the HI and risk addition formulas of these exposures used by the Superfund program relied on single chemical risk values readily available from EPA's Integrated Risk Information System (IRIS) database (U.S. EPA, 2007), the mixture assessment was feasible and continues to be widely implemented. While RAGs represents a significant step in the development of cumulative risk assessment methods, it does not discuss toxic interactions, the screening approaches for multiple pathways are minimally described and key details on how and when to use the total HQ concept are not presented.

1.3.1.3. Pesticide Group Cumulative Risk Assessment—Following the passage of the Food Quality Protection Act (FQPA) in 1996, 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, regardless of source. The resulting cumulative risk guidance includes a modified HI formula for the mixture aspect and an aggregate risk formula that is functionally similar to the total HQ 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 and 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, 2002c). 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). An issue not addressed in 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.

1.4. THIS REPORT'S APPROACH TO CUMULATIVE RISK ASSESSMENT

Many situations do not have a population focus or do not involve multiple chemicals and so would not need a cumulative risk assessment. However, there are certain scenarios which would naturally lead to conducting a cumulative risk assessment, denoted here as initiating factors. Figure 1-5 shows these three identified initiating factors along with the data elements that may be included in a cumulative risk assessment. These initiating factors are (1) multiple pollutant sources or releases, (2) elevated concentrations from environmental monitoring or biomonitoring of chemicals and (3) increased population illness in a community. Figure 1-6 illustrates the types of information that may be considered for data collection and population characterization and shows the relationship of this information to the initiating factors. It is noteworthy that traditional source-based assessments are usually initiated when chemicals are found or released into the environment from known sources. When this occurs, population vulnerability factors, such as diet, behaviors, genetic traits, economic status and social characteristics are often not included in the assessment. (See Text Box 1-3 for a discussion of the challenges related to expertise and

Challenges to Conducting Cumulative Risk Assessments
(Text Box 1-3)

A challenge to conducting cumulative risk assessments that include non-traditional stressors is identifying expertise in the risk assessment community for evaluating risks posed by such stressors and developing organizational support for such efforts. In the U.S. Federal Government, different Agencies have purview for related exposures; no individual Agency has as its mission to evaluate all chemicals and stressors together, so collaboration may become important. For example, the Food and Drug Administration is responsible for dietary stressors and pharmaceuticals, so collaborations with EPA would be useful regarding if and how these stressors would impact a population also exposed to environmental chemical pollutants. Furthermore, the development of a collaborative network with the medical community and industry (e.g., pharmaceutical companies) also would help to integrate environmental risk assessments with public health information, exposure data and dose-response study results on toxic chemicals and pharmaceuticals. Establishing cross-organizational workgroups and within-organizational structures would be an initial step towards conducting and completing cumulative risk assessments. Similarly, within the EPA, collaboration may become important among established organizational units, e.g., among the program offices for water, air, solid waste and pesticides.

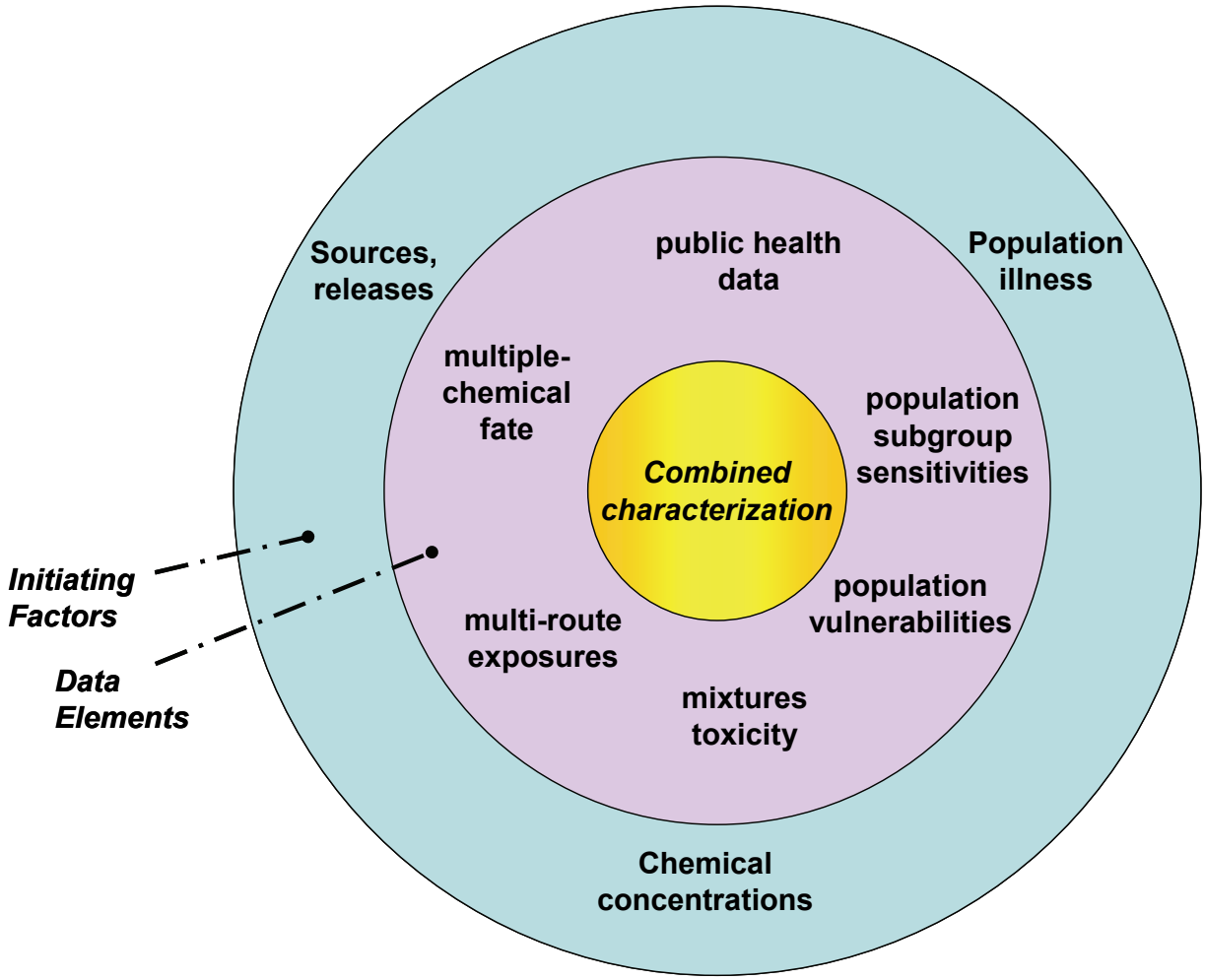


FIGURE 1-5
Common Initiating Factors and Elements of Cumulative Assessments

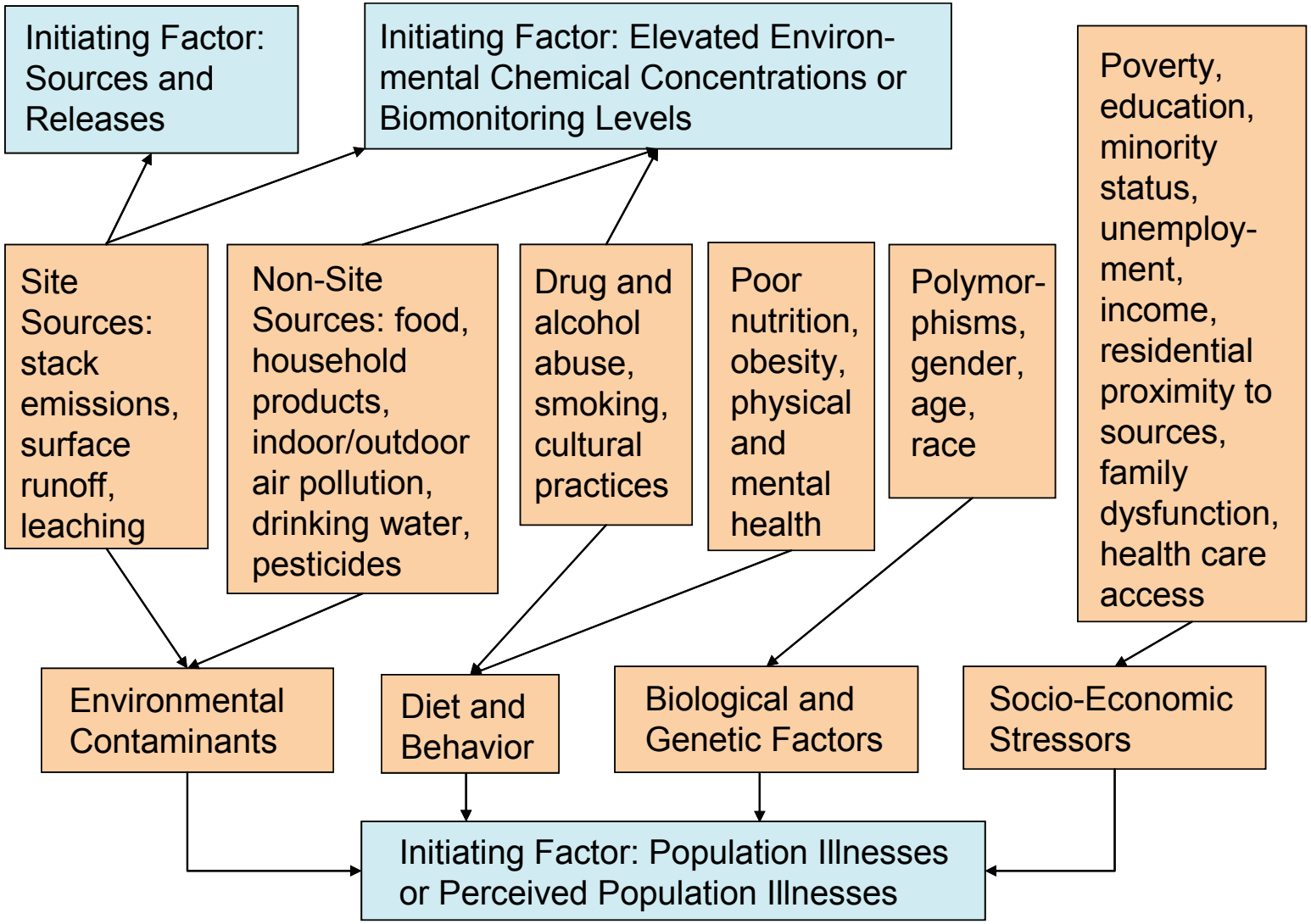


FIGURE 1-6

Variables Considered in Cumulative Risk Assessment and their Relationship to Initiating Factors

organizational structure when these non-traditional stressors are incorporated into an assessment.) These traits are more likely to be assessed when population illness or the potential for illness are the initiating factor.

Figure 1-7 shows the key steps in a cumulative risk assessment, with a primary focus of addressing multiple chemicals, pathways, timeframes and effects in a population-based setting. These steps define the population of concern and its study area, generate a list of environmental contaminants relevant to the initiating factor and identify links between environmental chemical exposures and vulnerabilities within the population. These steps form the initial collection and organization of information to focus on the cumulative aspects of the risk assessment. These steps may not be sequential and may involve a number of iterations as the analyst examines factors related to population vulnerabilities, public health information, toxicological and epidemiologic data, completed exposure pathways, differential exposures and contact with environmental media and pollutant sources. Outputs include a population profile, a list of relevant chemicals, chemical groups for use in risk analysis and characterization and a conceptual model. Outputs may include additional epidemiologic evaluations that assess the health of the community or that examine associations between health impacts and pollutant exposures. The activities in a cumulative risk assessment that are summarized in this chapter include:

- Characterize the population or community of concern and the study area based on the initiating factor
- Develop a list of relevant chemicals
- Compile information on exposure conditions and toxicity
- Identify population subgroups who are sensitive to the relevant chemicals or vulnerable to differential exposure
- Iterate those steps to improve the relevance of the exposure and population factors to the health risks of greatest concern
- Conduct a risk characterization, including uncertainty and sensitivity analyses.

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 information or event that initiated the cumulative risk assessment. For example, consider the case where awareness of multiple pollutant sources raises concerns of cumulative health risk. The data from EPA's Toxic Release Inventory (TRI) 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 to many of the initial

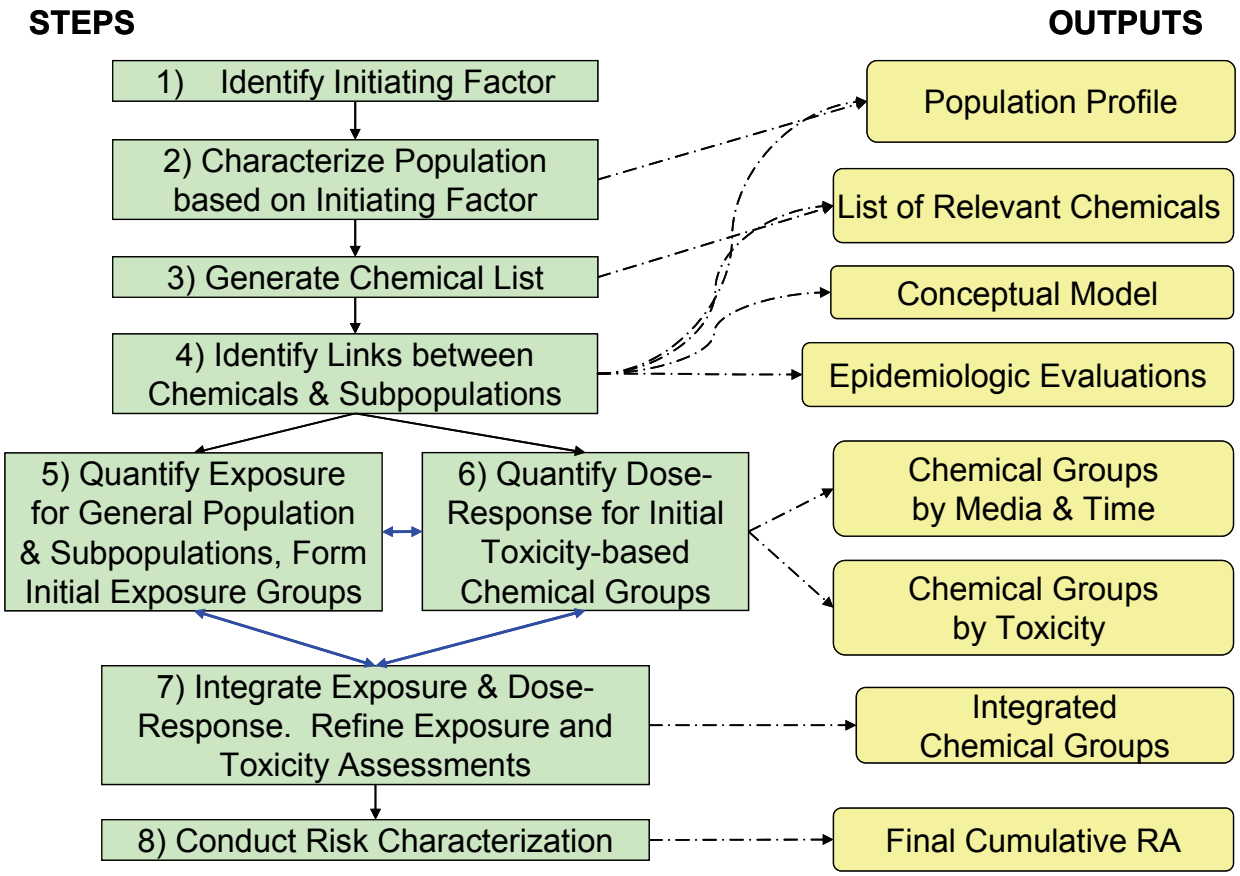


FIGURE 1-7

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

steps of cumulative risk assessment. In this chapter, the steps are briefly described in order to show their contributions to the cumulative risk assessment and their interconnections (Figure 1-7). Subsequent chapters have more complete discussions on exposure assessment (Chapter 3), toxicity assessment (Chapter 4), which are both part of the Risk Analysis phase and Risk Characterization (Chapter 5).

1.4.1. Technical Approaches for Multiple Chemicals, Exposures and Effects. Chapters 3, 4 and 5 deviate from the broad definition of cumulative risk assessment by providing technical methods for evaluating only multiple chemicals, exposures and effects. The approaches do not account for additional population variables, such as those that are associated with vulnerabilities (i.e., those factors in Figure 1-6 related to diet, behavior, genetics and biology, and social and economic factors). EPA does address a few of these factors (e.g., sensitive subgroups, children, elderly), however, it may be useful to conduct additional research on analyzing health risks for vulnerable populations and to collaborate with other organizations that may have access to relevant data (see Text Box 1-4). The intent of these three chapters and Appendices A, B and C is to provide a library of approaches and resources to more explicitly assess the multifactor aspects of cumulative risks for specific scenarios and sites. Because of the variability in these scenarios, such an assessment can involve evaluating many different sources and contaminants, several media (soil, water and air) 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 informative assessments of these sites and situations, leading to better decisions for managing potential cumulative risks.

Additionally, Chapters 3, 4 and 5 of this report provide a structured collection of approaches for addressing the chemical interactions and joint toxicity issues in cumulative risk assessment. Chemical and toxicological interactions are a primary focus because these are areas where methodological advances allow the traditional process (evaluating chemicals individually) to be enhanced. Approaches for chemical 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 causing adverse cumulative risks.

1.4.2. Identify the Initiating Factor for the Cumulative Risk Assessment. The initial stage of a cumulative risk assessment (Planning and Scoping) forms a systematic,

iterative process that defines the risk problem to be assessed and the technical elements to be emphasized (U.S. EPA, 2003a). The main backdrop for Problem Formulation and initial data review is provided by the regulatory context and the particular information or technical factors that led to the decision to consider undertaking a cumulative risk assessment. Three typical initiating factors include multiple pollutant sources within the community, increases in illnesses in the population and elevated chemical concentrations due either to monitoring of environmental levels or biomonitoring of chemicals in humans (e.g., in blood or urine samples). These initiating factors could occur in any community, but environmental justice considerations may cause a cumulative risk assessment to be undertaken more readily because of the proximity of a community to pollutant sources or cultural practices of a population that may cause it to be differentially exposed. Figure 1-5 shows these initiating factors and the common data elements that link the initiating factors with the population. These initiating factors can be displayed within the preliminary conceptual model that is developed during the Problem Formulation phase. The identification and discussion of initiating factors in the planning stages may improve the understanding of any links between the population risk estimate, which is the result of the cumulative risk assessment, and the initiating factor, which initiated the assessment.

After the initiating factor has been characterized, the next steps involve defining the population of concern and its study area, generating a list of environmental contaminants relevant to the initiating factor and identifying links between environmental chemical exposures and vulnerabilities within the population. Then, data are collected and organized with a focus on the cumulative aspects of the risk assessment. These steps, 2-4 in Figure 1-7, may not be sequential but may involve a number of iterations as the risk analyst examines factors related to population vulnerabilities, public health information, toxicological and epidemiologic data, completed exposure pathways, differential exposures and contact with environmental media and pollutant sources. Outputs from steps 2-4 include a population profile, a list of relevant chemicals and a conceptual model. They may also include additional epidemiologic evaluations that assess the health of the community or examine associations between health impacts and pollutant exposures.

1.4.3. Characterize the Community and Population Based on the Initiating Factor.

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 geographic features, such as a lake and surrounding watershed. The population may be a neighborhood or the community in an entire city, perhaps an Indian reservation or the public using a resource, such as a lake. The population description would also include sensitive or susceptible subgroups based on increased exposure, genetic or physical traits or vulnerability. This description may include cultural practices or housing locations that differentially affect a population's exposure. If population illness is the initiating factor for the cumulative risk assessment, then it would be consistent with good epidemiologic practices to determine the extent of the morbidity or mortality and the uniqueness of the disease or the disease rates in comparison to baseline levels in other communities. Often the definition of the population and study area could be influenced by the initiating factor. Because a cumulative risk assessment is population-focused so that all relevant exposures and effects are considered, as the potential exposures and health effects are further investigated, the population characterization will be refined.

1.4.4. Generate Initial List of Relevant Chemicals. The *Framework* distinguishes cumulative risk assessment from traditional risk assessments by its population focus. Consequently, once the initial population description is complete, including population demographics and the boundaries of the study area, information on chemical releases, biomonitoring data, public health information and environmental concentrations are evaluated in light of the identified population to develop the initial list of relevant chemicals (see discussion in Text Box 1-4 where it is recognized that other confounding factors may also be responsible for health effects in the population). Existing 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 list of relevant chemicals is likely to be closely tied to the initiating factor. The influence of the initiating factor is discussed in more detail in the exposure assessment chapter (Chapter 3).

Chemical and Stressor Involvement in Cumulative Risk Assessment *(Text Box 1-4)*

When a cumulative risk assessment is initiated by health effect(s) in the population, and there is reason to believe an environmental exposure may be the cause, the initial goal of the investigation is to determine if environmental chemicals present in the affected community can be linked to those health endpoints. It may be noted that other stressors within the population may be responsible for either causing health effects or for contributing to their expression in conjunction with chemical exposures. Examples of such confounding factors include contributions to various cancers from smoking, hearing loss from co-exposure to noise and chemicals and associations between high blood pressure and stress. As such, investigators conducting a cumulative risk assessment may find it useful to make note of such stressors that may contribute to occurrence of a health endpoint in addition to developing a list of relevant chemicals. This information can then be taken into account during uncertainty analysis and risk characterization.

1.4.4.1. Use Program and Regional Office Procedures — Determination of relevant chemicals is covered in several guidance documents from the EPA Program Offices (e.g., Office of Water, Office of Pesticide Programs, Office of Solid Waste and Emergency Response, Office of Air Quality, Planning and Standards) and Regional Offices (see Appendix A). For exposures by multiple media, the chemicals may be identified using approaches from several programs or guidance from EPA's ORD (e.g., U.S. EPA, 1996a). The initial chemical list may be overly inclusive to allow for the examination of potential interactions from joint exposures so that joint toxicity can be evaluated in later steps of the assessment. For example, a chemical could be evaluated based on the ratio of its exposure level to its safe level, i.e., its HQ. A chemical that might be screened out in a single chemical assessment because its HQ is less than 1 might be retained in a cumulative assessment (e.g., unless it's HQ is less than 0.1) in order to allow for potential dose additivity or interactions.

1.4.4.2. Identify Chemicals Related to the Initiating factor — The three types of initiating factors in this report have only subtle differences in their influence on the chemical list. When health endpoints are the initiating factor, 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, biomonitoring data or pollutant sources are the initiating factor, the preliminary chemical list could at first be restricted to those measured or likely to be found in environmental emissions. Those that lack toxicity information or are initially deemed unlikely to pose significant health risks based on human or animal data may be placed on a *watch list* pending further analysis during the iteration of the exposure and toxicity assessment steps. Chemicals known to be similar to or toxicologically interactive with those on the preliminary chemical list might then be added if their exposure to the identified population is considered plausible, such as similar chemicals in food. It is consistent with chemical mixtures risk assessment practices to consider multiple endpoints for each chemical, not just the critical effect used to define the EPA's IRIS risk values (U.S. EPA, 2007) to allow for determination of potentially interactive chemicals. 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.

1.4.5. 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 examine the potential for exposures and differential exposures to those chemicals among population groups, including sensitive or vulnerable population subgroups in the defined population of concern. Certain population groups may be particularly sensitive to toxic chemicals because of higher exposure or increased vulnerability. Higher exposures can often be estimated by considering lifestyle information (e.g., U.S. EPA, 1997a) and occupational data (e.g., as conducted by the National Institute for Occupational Safety and Health http://www.cdc.gov/niosh/homepage.html). One difference for cumulative risk assessment is that elevated exposures can include the combined exposure to multiple toxicologically-similar chemicals, such as chemicals in the 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 lead to additional sensitive population subgroups (Figure 1-6). Vulnerability can be more complex, ranging from existing disease (e.g., hospital patients, individuals receiving outpatient treatment) 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 the foci of current research.

The chemical list may 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 initiating factor. Such a table might be arranged as follows:

- Tier 1 Chemicals are linked directly to population subgroups through biomonitoring and are identified in emissions from one or more sources
- Tier 2 Chemicals are linked indirectly to population subgroups by association with elevated disease in the population and are identified in emissions from one or more sources
- Tier 3 Chemicals are linked to sensitive subgroups of the population of concern based on human data and are identified in emissions from one or more sources
- Tier 4 Chemicals are linked to sensitive subgroups of the population based on extrapolations from experimental animal studies and are identified in emissions from one or more sources
- Tier 5 Chemicals are identified in emissions from one or more sources and are identified by their potential for joint exposure (e.g., by multiple routes) or joint toxicity with other chemicals on the list

Tier 6 Chemicals are identified in emissions from one or more sources but lack toxicity information or are initially deemed unlikely to pose significant health risks based on human or animal data; these chemicals are placed on a *watch list* pending further analysis during the iteration of the exposure and toxicity assessment steps

1.4.6. Quantify Human Exposures for Initial Exposure Grouping. Up to this point, there has been no actual exposure assessment, only a listing of chemicals. Extensive EPA documents provide guidance 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, 2005b) along with programmatic guidance on Superfund sites and multiple pesticide exposures (U.S. EPA, 1999a,b). In general, the assessment might rely on 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 (NCEA; 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. EPA, 2005b) and dermal exposure to soil is covered by the supplemental OSWER guidance (U.S. EPA, 2004a).

Quantification of exposure for cumulative risk assessment begins with a clear definition of the population and study area so that the analyst can identify all existing and future completed pathways. Monitoring data for chemical concentrations and information from epidemiologic studies or public health databases may be used as starting points for any exposure modeling that is done. The assessment may also identify the relevant exposure factors, with particular attention to unique factors for the sensitive subpopulations; such factors, e.g., cultural practices, may be used to adjust the exposure assessment based on differential exposures. Once the exposure is characterized for the population of concern and its sensitive and vulnerable 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 timing and either medium or pathway (see Chapter 3 for details).

Any issues that cannot be quantified may 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 or vulnerable subpopulations.

1.4.7. Quantify Dose-Response for Initial Toxicity Grouping. The focus of toxicity assessment regarding cumulative risk revolves around timing issues of exposure and toxicity. The chemical grouping resulting from the exposure quantification (by timing, media and pathway) is 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.

During this step, chemicals previously put on the *watch list* may be re-evaluated by considering the potential or expected toxicities at the estimated exposure levels. Toxicological interactions could be further considered for the watch list chemicals, 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 may be described qualitatively, especially regarding importance to potential health effects in the sensitive subpopulations.

1.4.8. Integrate Exposure and Dose-Response Information. In this final analysis stage, the exposure assessment is interfaced with the dose-response assessment in order to refine the information on joint exposures of main toxicological 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 are highlighted for consideration of improvements in the exposure information. Ideally, this step would occur throughout the assessment process. 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.

1.4.9. Conduct Risk Characterization. A Risk Characterization is usually described in 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

focuses on recommendations and uncertainties. Figure 1-8 provides an overview of the final Risk Characterization process. It is an expansion of the final Rick Characterization step shown in Figure 1-7, beginning with outputs from the steps shown in Figure 1-7, such as, the population profile and the integrated chemical groups. Figure 1-8 is presented again in Chapter 5 (as Figure 5-1) and explained in greater detail. The cumulative Risk Characterization may differ from a traditional Risk Characterization in several 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 listed below:

- Recommendations could be multivariate, i.e., the analyst might not be able to identify a single chemical, pathway or critical effect that drives the risk
- Recommendations might be based on groupings of chemicals, pathways and effects, but such groupings can be based on subjective judgments
- Recommendations might be based on epidemiological findings relevant to a population illness, for which it is useful to articulate confounding factors and exposure uncertainties
- Uncertainty analysis might be predominantly qualitative because of the use of 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

1.8. SUMMARY

Many site and situation health risk assessments can be adequately addressed using single chemical and single pathway evaluations. At other sites and in other situations risk analysts may choose to evaluate population vulnerabilities, multiple chemicals and complex exposures; in these cases cumulative risk assessments will be undertaken. Many basic cumulative risk concepts—including consideration of multiple sources, chemicals and exposures—are in the standard guidance from the last 15 years. This report builds on those standard 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 risk assessment.

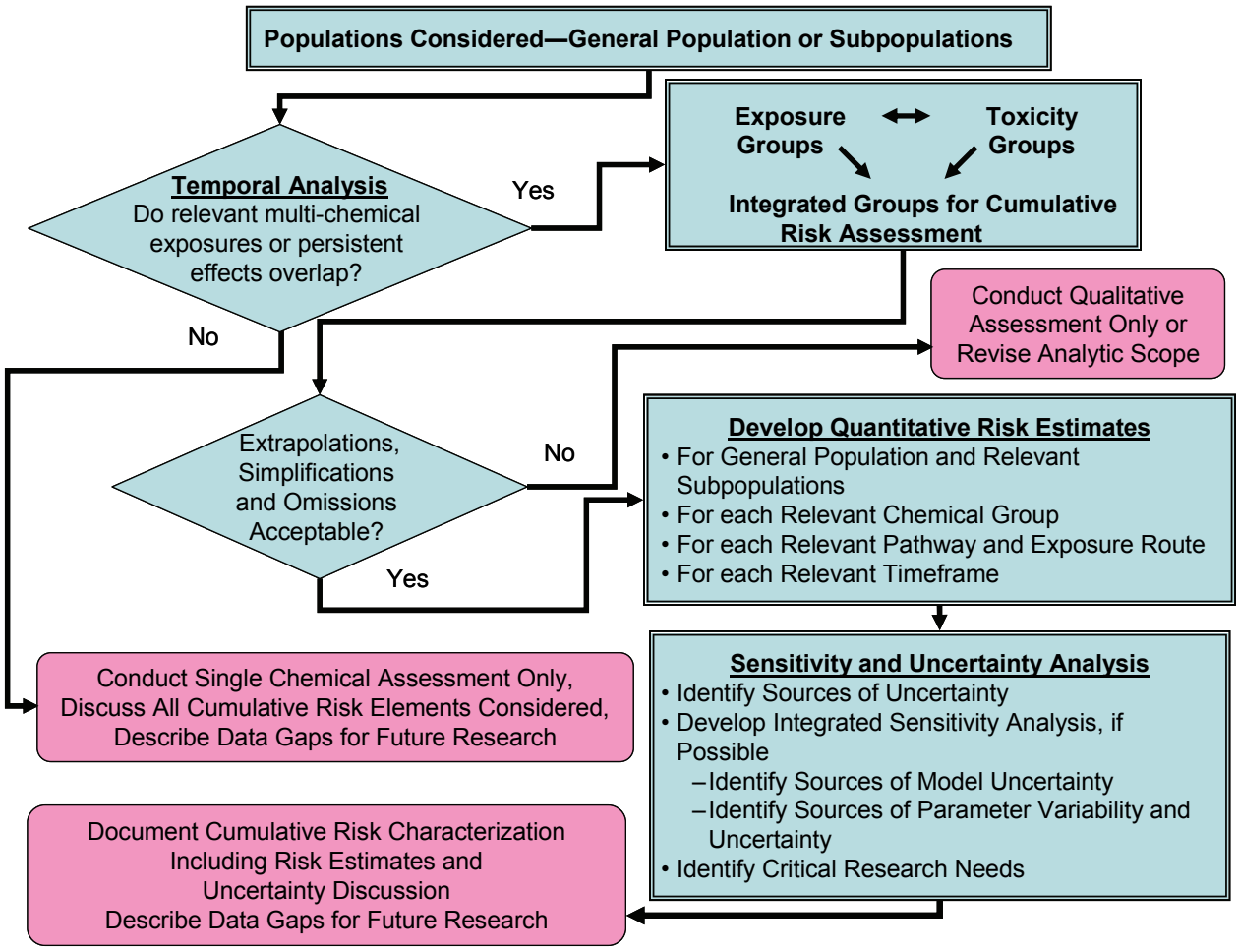


FIGURE 1-8
Schematic of Cumulative Risk Characterization Approach in this Report

2. IDENTIFICATION OF INITIATING FACTORS, POPULATION CHARACTERISTICS, DATA COLLECTION AND ORGANIZATION

This report has identified three initiating factors of a cumulative risk assessment. These include multiple pollutant sources within the community, increases in illnesses in the population, and elevated chemical concentrations, due to either monitoring of environmental levels or biomonitoring of chemicals in humans. Figure 2-1 shows examples of these initiating factors and of the data elements that may be considered in a cumulative risk assessment. This chapter discusses these initiating factors and data elements and shows their interconnections. Section 2.1 describes the initiating factors. Sections 2.2 and 2.3 describe the preliminary evaluations of population and exposure information including the influence of the initiating factors on those evaluations. Section 2.4 discusses the importance of incorporating public health data on a community into the cumulative risk assessment. Section 2.5 describes epidemiologic approaches to addressing community concerns when a cumulative risk assessment is initiated. Section 2.5 describes the linking of population and exposure information to identify any subgroups within the population that would be sensitive to effects from those exposures and the use of conceptual models to help organize the information and analysis. Chapters 3-5 provide a more detailed evaluation and quantification of exposure, dose-response, the interface between these, and then the cumulative Risk Characterization.

2.1. INITIATING FACTORS FOR CUMULATIVE RISK ASSESSMENT

2.1.1. Health Endpoint as the Initiating Factor. When there is a perceived or documented increased incidence of one or more health effects in a community with no clear cause, there can be a demand for an investigation by the public. Initial investigations should focus on examining whether the health endpoints are, in fact, elevated. If an increased incidence of disease is not found, or if the elevated rates are considered a statistical artifact, then further investigations may not be warranted. If additional investigations are needed, then exposure assessments may be conducted either separately or as part of an epidemiologic study. Many health endpoints have been associated with several possible chemical causes, so these investigations may initiate a cumulative risk assessment. For example, in the 1970s a cluster of leukemia cases in Woburn, Massachusetts initiated exposure assessment studies (Durant et al., 1995; Parker and Rosen, 1981) and epidemiologic investigations (Lagakos et al., 1986; Cutler et al., 1986; Public Health Service, 1981; Telles, 1981) in the area. Although the eventual focus was on trichloroethylene exposures, an initial investigation focused on

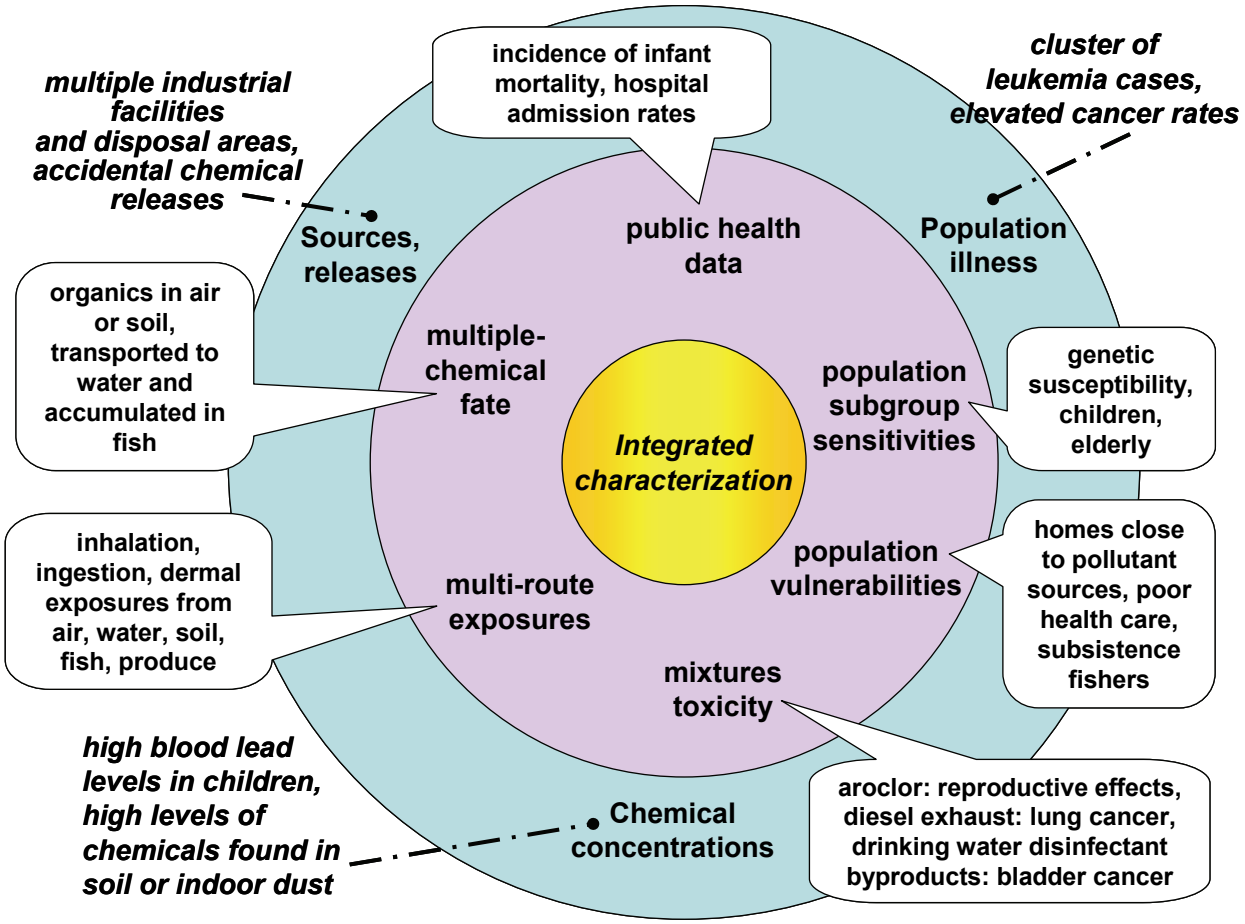


FIGURE 2-1
Example Initiating Factors and Data Elements for Cumulative Risk Analyses

several organic compounds while a later study investigated metal exposures (U.S. EPA, 2005a). In many cases, existence of higher than expected health effects (based on disease prevalence or incidence measures) 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 peer-reviewed data published in scientific journals. An examination of the details and the quality of initiating factor information by stakeholders and investigators is a primary objective of the Planning and Scoping stage.

2.1.2. Chemical Concentrations as the Initiating Factor. The detection of toxic chemicals in the environment, or in the human body, at elevated concentrations may initiate a cumulative risk assessment. For example, elevated levels of urban smog due to ground level particulates and ozone can frequently lead to public health intervention (e.g., advisories for young children and elderly to stay indoors). When community members become aware that such exposures may be combined with elevated chemical concentrations in soil and groundwater (e.g., heavy metals), a cumulative risk assessment may be conducted, such as the Cumulative Risk Initiative for Cook County, IL and Lake County, IN (see U.S. EPA, 2003a, p. 32).

What is considered "elevated" may be situation specific and could be determined through various interactions among environmental engineers, regulators, exposure analysts and toxicity experts. For example, exposures to environmental contaminants may be higher than engineering goals, exceed regulatory levels issued by various Agencies (see Appendix B for examples), or be of concern based on positive toxicological data either on single chemicals or from studies where several of the chemicals have been studied as a mixture. As when health effects are the initiating factor, it is important to document the quality and variability of the concentration data and whether such measurements indicate possibly complete exposure pathways for use in the Risk Analysis and Risk Characterization phases. Available concentration data have even greater influence in initiating a cumulative risk assessment when there are elevated levels of additional chemicals elsewhere, such as in food, that also impacts the same population. For example, in the 1990s, elevated levels of 2,3,7,8-chlorine substituted polychlorinated dibenzo-*p*-dioxins (PCDDs) were found in fryer chickens as the result of a contaminated mineral additive (i.e., ball clay) in their feed (Ferrario et al., 2000); such an exposure in the population's food supply would be important to consider in a cumulative risk assessment with additional exposures to PCDDs from other sources.

Biomonitoring data may also serve as a cause for health concerns for a given community. The Center for Disease Control (CDC) has published its third *National Report on Human Exposure to Environmental Chemicals*, which provides an assessment of the exposure of the U.S. population to environmental chemicals using biomonitoring (CDC, 2006). Through the National Health and Nutrition Examination Survey (NHANES), which is a series of surveys designed to collect data on the health and nutritional status of the U.S. population, the CDC measures levels of chemicals or their metabolites in blood and urine samples from randomly selected participants. This report includes exposure data for the U.S. population for 148 environmental chemicals over the period 2001-2002 and can be used to compare these national distributions with levels measured in a given community. If elevated levels of toxic chemicals are observed in biomonitoring data (e.g., elevated blood lead levels) in a specific community, then information may be gathered to examine increases in morbidity or mortality in the community or potential sources of exposure to such pollutants. Although biomonitoring for toxic chemicals may not be as routine as sampling for chemical concentrations, collection of such data is becoming more frequent and may be useful in identifying community concerns and potential health risks.

2.1.3. **Multiple Sources or Release Events as the Initiating Factor.** Multiple sources of chemical contamination can be an initiating factor for a cumulative risk assessment, often when they are the pending 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 conservation groups, ranging from lawsuits to scientific sampling of the water and biota (Richardson, 2004).

For a cumulative risk assessment initiated by a multiple sources or release events, one of the first activities is to identify all relevant sources of potential exposure to the population of concern, particularly sources releasing chemicals similar to those in the sources. For example, an investigation into possible pesticide drift to a residential neighborhood from nearby farms may warrant a concurrent evaluation of exposures from household use of similar pesticides by rural residents in the geographic area of concern.

2.2. 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 assessment begins 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 the population may be chosen simply to reflect locations of concern to U.S. EPA or to stakeholders. These locations can range from school yards or parks to homes and Native American lands. During this process, vulnerabilities of the population may be identified, including sensitivities and susceptibilities, general health and nutritional status, and factors that may cause differential exposure (e.g., lifestyle factors, cultural practices, dietary factors such as subsistence fishing, activity patterns and proximity of homes, playgrounds or farms/gardens to a pollutant source, etc.). Under this approach, vulnerable subpopulations can be identified and exposures traced back to evaluate all pathways by which a given subpopulation could be exposed to a variety of chemicals. As described in the EPA's *Framework* document, this approach is often applied to community-based cumulative risk assessments (U.S. EPA, 2003a). It can also play a role in other applications that are typically source-based. For example, the assessments for contaminated sites could use a population-based approach to address a specific group for which unique exposure or vulnerability/susceptibility issues are of concern (see Chapters 3 and 4). The analysis plan for a cumulative risk assessment could then reflect a combination of source- and receptor-based approaches.

When considering health effects in the population, the cumulative risk assessment addresses both existing health effects found in actual populations and also the potential for effects that may occur in later years (e.g., cancers that are expressed only after a long latency period). This is consistent with current Agency practices, for example, in Superfund site assessments where risk assessments evaluate health risks based on both current and future land uses and possible exposure pathways in the present and in the future (U.S. EPA, 1989a). When a cumulative risk assessment initiating factor is tied to a specific population (e.g., actual or perceived elevations in adverse health effects or the presence of chemicals found through biomonitoring), then the population may be specifically characterized by different vulnerability factors such as age distributions and other socio-demographic data. However, an equally important case occurs when a cumulative risk assessment initiating factor does not necessarily point to a given population or community, e.g., multiple pollutant sources are in a

general area or levels of monitored environmental chemicals are increased. This population at risk may not be easily identified initially, but may still be at potential risk of expressing health effects at some time in the future. Thus, although it is preferable to characterize existing populations with known exposures to environmental chemicals and observable health conditions, there is a need to define future populations with expected or anticipated exposures to environmental chemicals which may have uncertain impacts on human health. In either case, a cumulative risk assessment may be appropriate given community interests and perceptions and if the weight of evidence suggests that exposures to multiple chemicals may lead to significant health effects in the population of interest.

2.2.1. Preliminary Characterization of the Population Based on the Initiating Factor. The initial population characterization usually includes a description of the study area and the relevant population. The initiating 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 population subgroups. Alternatively, the initial population could be those in frequent contact with a geographic area, such as a park or lake. However, sometimes the stakeholders and analysts agree after further evaluation that the initiating factor is of lesser significance, and that another initiating factor will be the key motivation for continuing the cumulative risk assessment. The initial description of the study area and population of concern are considered to be preliminary and are subject to change during the course of the risk assessment.

2.2.1.1. Population Defined by the Health Endpoint — If a population group is associated with the health effect initiating factor, then this group would automatically be included in the initial population of concern. For example, if the initiating factor 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 certain sensitive subgroups could be further examined (e.g., asthmatic schoolchildren). 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 initiating factor health endpoints (as well as other endpoints) and chemical exposures.

2.2.1.2. Population Defined by Chemical Concentrations — When elevated environmental chemical concentrations are detected, the monitoring locations can act as initial 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 release sites or monitoring locations. When elevated biomonitoring data are detected, then the homes or business locations of those people being tested can act as initial bounds of the study area. If feasible, determining the source(s) of the chemicals found in biological samples (e.g., in blood or urine) may be a priority. Identification of the source(s) would then provide information to further refine the study area and population at risk for the study.

Chemical concentrations limited to specific resources or geographic features can define a study population according to those with likely access to that resource or location. Contamination of a recreational lake might lead to the population being defined as those known and potential users of the lake; this might include recreational anglers and their families and friends who might consume fish caught in the lake. At this stage, the identification of sensitive population subgroups might be based only on known sensitive groups in the defined population.

2.2.1.3. Population Defined by Multiple Sources — When multiple sources are the initiating factor, exposures have typically not yet been estimated. The initial boundaries of the population of concern then might be roughly defined by possible dispersion or deposition characteristics of existing and possible future emissions as well as populations with possible future exposures (U.S. EPA, 1998a). The initiating factor sources could initially be considered in isolation. As the assessment proceeds, the refinements would consider all sources so that each pollutant source would be evaluated both for its individual incremental population risk as well as in the context of combined risk with other sources.

2.2.2. Refining the Population Profile Based on Vulnerable Subpopulations. Once the initial population characterization and study area have been defined, vulnerabilities within those populations may be identified in a cumulative risk assessment. EPA's *Framework* 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 (e.g., disease immunizations), 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. Once the potential vulnerability factors are identified, risks may be calculated separately for populations with specific receptor characteristics. Risk assessments stratified by subpopulations can be conducted in a stepwise manner, beginning with single chemical assessments for that subpopulation and expanding the analysis to examination of risk associated with cumulative exposures.

Epidemiologic studies often involve examination of whether certain receptor characteristics (i.e., vulnerability factors) contribute to the toxicity caused by chemical mixture exposures. If certain factors may confound associations of interest they are addressed by statistical adjustment or through specific design features. Effect measure modification may also be considered if vulnerability factors modify the main association between exposure and disease. For example, Perera et al. (2003) reported differential effects of polycyclic aromatic hydrocarbons(PAH)-related exposures with lower mean birth weight and smaller head circumference among African Americans versus Dominican infants born in New York City. These data suggested that minorities may be differentially exposed to environmental tobacco smoke (ETS), increasing their susceptibility to environmental PAH levels. Additional research showed a multiplicative effect between ETS exposure and a molecular marker of PAH exposure (benzo [*a*] pyrene-DNA adduct), despite no PAH-related developmental effects in the absence of ETS (Perera et al., 2004). For a cumulative risk assessment, a factor such as differential exposure to ETS may be taken into account when evaluating the potential health effects of an environmental mixture. In the assessment of rural communities, the literature suggests that impacts from exposures to mixtures of pesticides may be evaluated from a cumulative risk perspective (see Text Box 2-1).

2.3. INITIAL ASSESSMENT OF EXPOSURE DATA

Once a cumulative risk assessment is initiated and the population and study area are defined, an initial exposure assessment is conducted. 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 initiating factor. It also discusses specific population data to be collected initially in order to conduct the exposure assessment. Chapter 3 discusses specific approaches to cumulative exposure assessment.

2.3.1. Initiating the Exposure Assessment when Health Endpoint is the Initiating Factor. When an increased incidence of health endpoints initiates an assessment, and exposures to environmental chemicals are suspected to be the cause, the initial goal of the investigation is to determine if environmental chemicals present in a community are linked in some way to those health endpoints. Specific populations may also be evaluated for sensitivity to the identified health effects, the potential for chemical exposures to exacerbate an existing condition in sensitive or vulnerable individuals or people who may have an impaired ability to resist these specific illnesses due to social factors (e.g., poor nutrition or health care access). These types of analyses are similar to epidemiologic investigations, such as those conducted to determine *if* and *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 initiating factor which was initially attributed to general organophosphate poisoning but later focused on exposure to a single pesticide. In this case, a sensitive subpopulation, i.e., a group of children, who may have also been differentially exposed due to their activity patterns, became ill due to an illegal pesticide application.

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). One component of this study examines the impacts of lifestyle, cultural, ethnic and genetic factors (i.e., vulnerability 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, resulting in more pesticide-related health effects in white farmers than in black farmers. The higher pesticide exposures may be explained by farm characteristics or economics (Martin et al., 2002) and
- association of specific pesticides (i.e., paraquat, parathion, malathion, chlorpyrifos, thiocarbamate) with respiratory symptoms of farmers (Hoppin et al., 2002).

Health registries can serve as important resources for evaluating the potential health impacts of environmental exposures for cumulative risk assessments. For example, most states maintain cancer registries, as do national organizations and some federal agencies, e.g., the National Cancer Institute. Birth defect registries also exist in over 30 states, but the quality of most data in these registries is considered inadequate

for an effective tracking program (EHTPT, 2000), particularly regarding the implications of linking such effects with environmental exposure to multiple chemicals.

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

Information reported to health officials	Seven siblings presenting with abdominal pains and respiratory arrest, symptoms of organophosphate poisoning. Two children died.
Setting observations	Adult resident recently sprayed an unknown insecticide in the home.
Investigative discovery	Illegal pest-control application of methyl parathion inside home at 3 times the concentration used in agricultural spraying (this OP 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 (e.g., blood or urine samples) to identify people exposed (multi-pathway).
Risk management action	Decontamination of house and increased publication of dangers of inappropriate OP uses.
Source	CDC (1984).

For health endpoints initiating factors with suspected environmental etiologies, the initial phase of the risk assessment involves a data 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 or in an occupational epidemiologic study). 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 of both toxicological and epidemiologic data. Because multiple chemicals are involved, it is consistent with best risk assessment practice to include both critical (primary) and other secondary effects in the literature review. 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, while secondary effects are typically those seen at higher doses in the same target organ or tissue and/or different physiological compartment(s). For example, the acceptable level of a chemical to which humans may be safely exposed could be based on hepatotoxicity, the most sensitive endpoint identified in a toxicological bioassay, but the available literature indicate that the chemical is also a potential reproductive toxicant at doses higher than those where hepatotoxicity was observed. This 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 exposure measurements and analysis. In summary, the goal of this first step is to determine the pollutants of concern (either individually or in groups)

TABLE 2-1

Examples of Illnesses Possibly Linked to Multiple Environmental Factors[a]

Illness/ Health Effect	Hypothesized Causes/ Epidemiologic 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. These levels exceed the U.S. occupational 8-hour standard of 1 ppm for benzene in air.	Benzene is present in gasoline, automobile exhaust and cigarette smoke. The latter 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

TABLE 2-1 cont.

Illness/ Health Effect	Hypothesized Causes/ Epidemiologic 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, 2007; Amdur et al., 1993
Liver cancer	Many (>100) chemicals and risk factors, 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 4.4-11 becquerels/m^3.	Tobacco smoke is the leading cause of lung cancer. Lung cancers increase multiplicatively when radon exposure occurs in addition to cigarette smoking.	NTP, 2002
Neurological damage/ reduced intelligence quotient (IQ)	Lead in lead-based paint; mixtures of polychlorinated biphenyls (PCBs) and dioxins; fetal irradiation; methylmercury.	An increase in blood lead levels from 10-30 µg/dL resulted in an IQ reduction of 4-5% (4.4-5.3 points) in 7-year-old children. Increased maternal blood mercury concentrations or hair mercury	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; Kjellstrom et al., 1986, 1989; Grandjean et al. 1997; Crump et

TABLE 2-1 cont.

Illness/ Health Effect	Hypothesized Causes/ Epidemiologic Links	Associated Levels	Remarks	Reference
		concentrations resulted in IQ reductions in 6-year old children (regression coefficient -0.5 IQ pts/1 ppm increase hair mercury)		al.,1998
Parkinson's Disease and Parkinsonism (which can be reversible)	Many pesticides, including organophosphates, organochlorines, carbamates, various herbicides and household fumigants; manganese, carbon monoxide and carbon disulfide	Increased risk of 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 using well water and living in farming areas, especially those with a history of pesticide exposure. Higher levels of organochlorine pesticides in brain tissue from Parkinson's patients than the general population. Idiopathic [b] causes account for >85% of all cases; suspected links exist to MPTP,[c] organomercury, encephalitis, major tranquilizing drugs, carbon monoxide or disulfide poisoning and frequent head injuries.	Feldman, 1992; Gorell et al., 1999; Wright and Keller-Byrne, 2005; Stephenson, 2000; Engel, 2001

[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 initiate a cumulative risk assessment concern because of the number of possible chemical causative agents and their likely joint toxicity.

[b] Idiopathic is defined as having an unknown cause.

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

that have been linked to the initiating factor effect and similar health effects and to identify the combinations of subpopulations and pollutants of concern that might require more detailed exposure assessment because of higher exposure and/or enhanced toxicity in those subpopulations.

2.3.2. Initiating the Exposure Assessment when Elevated Chemical Concentrations are the Initiating Factor. When increased environmental chemical concentrations or biomonitoring results initiate a cumulative risk assessment, the initial goal of the investigation is to determine if those concentrations could result in exposures or doses that could lead to potentially important health effects in the community, including secondary health endpoints and the potential for effects due to toxicological interactions among chemicals. In addition, the population profile for the community may be examined to identify any increased incidence of morbidity or mortality measures that may be considered during the exposure assessment. 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, 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 initiate 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 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 are identified. Because a cumulative risk assessment is being initiated, the investigation includes an evaluation of the potential for other chemical exposures in the community that could increase the toxicity of the chemicals known to be at high concentrations. This could involve an examination of potential sources of pollution in the community (e.g., using the Toxic Release Inventory reports on pollutants typically released from industrial sources) followed by monitoring of related environmental media. Other EPA documents (e.g., *Human Health Risk Assessment Protocol for Hazardous Waste Combustion Facilities*

[U.S. EPA, 2005b]) can further aid in the 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 multi-chemical exposures among chemicals with high environmental concentrations or elevated biomonitoring levels;
(2) to characterize the primary and secondary health effects potentially associated with those chemicals and identify any related morbidity or mortality in the population; and
(3) to determine if there are other pollutants (either individually or in groups) to be monitored in other media (e.g., household pesticide use) because of their influences on exposure or because they produce similar health effects.

2.3.3. Initiating the Exposure Assessment when One or More Sources is the Initiating Factor. When one or more sources initiate a cumulative risk assessment, the initial goals of the investigation are to determine if the chemicals released from those sources could cause exposures high enough to cause health effects in the community and to examine the community's population profile to identify any increased incidences of morbidity or mortality that may be considered during the exposure assessment. With multiple sources it is important to determine which chemicals from those sources will reach the population(s) of concern. 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). 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 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) and the *Human Health Risk Assessment Protocol for Hazardous Waste Combustion Facilities* (U.S. EPA, 2005b). 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 initiate a cumulative risk 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. Different types of sources may be involved, so that exposure assessment guidance from several U.S. EPA Program Offices might have to be consulted. Most of these 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, 2005b, 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 examination of other sources, including nonpoint sources, of specific pollutant exposures to the community may also be considered. In conjunction with dose-response analyses, the primary and secondary health effects associated with the individual chemicals or groups of chemicals are identified so that the exposure assessment can provide information to categorize the identified chemicals from multiple sources into groups 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.

2.3.4. Summary. During the initial assessment step, the focus of the cumulative risk assessment is on determining what emissions sources, chemicals or population locations to include and what chemicals to evaluate together. The population profile for the community is also being examined to identify any increased incidence of morbidity or mortality measures that may be considered during the exposure assessment. In evaluating which chemicals are of concern for a community, it is useful to consider the specific initiating factors of the cumulative risk assessment and any issues, sensitivities or vulnerabilities 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 EPA Program Offices typically include

- toxicity;
- mass released or mass 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 and
- the potential for relatively high exposures to sensitive or vulnerable populations.

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

- 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;
- specific genetic traits or other physical characteristics of the population that would increase susceptibility to chemicals linked to the illnesses observed in the population;
- cultural practices that might cause the population to be differentially exposed to a chemical or group of chemicals;
- public health monitoring data and
- chemicals that may be linked to illnesses or exposures in identifiable population subgroups such as children or the elderly.

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

2.4. INTEGRATION OF PUBLIC HEALTH INFORMATION

Regardless of the initiating factor, it may be useful to collect and evaluate available public health information relevant to the investigation and to the identified population. Examples of such data include cancer and other disease rates, blood lead levels, hospital admissions, and mortality records. Such information can be used for comparison with initiating factor data, e.g., to verify suspected health effects given the chemicals found in the environment or, conversely, to explain health effects in a community that may not be caused by chemical exposures.

Public health information was used in a community-level investigation in Chester, PA (U.S. EPA, 2002b) after the EPA was approached by community representatives regarding possible excessive chemical exposures (e.g., to diesel emissions and drinking water disinfection by-products) and health effects (e.g., cancer). As part of the cumulative risk assessment that was conducted, EPA used public health information, examining blood lead levels and also comparing disease rates between Chester and the state of Pennsylvania. In both males and females respiratory cancer rates in Chester were found to be much higher than the state average. Incidence rates for leukemia, prostate cancer, and all cancers combined were statistically significantly higher for males compared to incidence rates for the state, the county and Philadelphia. EPA also identified a serious public health problem in Chester by examining venous blood lead test level results for 6783 children over a 5-year period. Results indicated that approximately 50% of the children tested had blood levels in the range where lead poisoning is a concern and approximately 67% had blood lead levels above the accepted level of concern of 10 µg/dl (U.S. Consumer Product Safety Commission, 2005). These two investigations using public health data confirmed that adverse health effects were being observed in Chester, PA. As a result, the cumulative risk assessment included all identified carcinogens, lead and other environmental chemicals as relevant chemicals to being evaluated.

2.5. EPIDEMIOLOGIC INVESTIGATIONS IN CUMULATIVE RISK ASSESSMENT

Different approaches to the cumulative risk assessment may be necessary depending on the type of initiating factor that is identified. When population illness is the initiating factor, an epidemiologic investigation may be warranted to ascertain, if possible, the relationship of environmental or other exposures (or stressors) to the occurrence of illness. When the initiating factor is a particular source, environmental concentration or biomonitoring result, the investigation may apply epidemiologic methods that include an examination of chemicals and their sources. In general, many health effects can have multiple risk factors and the process of attributing risks to individual stressors is often complex. An example that reflects this multi-factorial risk perspective is an impoverished population whose principal diet is fish and foods with high fat content, with a subpopulation characterized by lifestyle risk factors such as alcohol abuse and smoking. The population may have elevated heart disease and cancer rates that could be due to dietary or other behavioral risk factors and/or environmental exposures, yet the community focuses their concerns on environmental

exposures. The initiating factor (e.g., elevated cancer mortality) in this case may be addressed by an epidemiologic investigation. When health endpoints are initiating factors for cumulative risk assessment, the analytic methods may need to be in context of this multi-factorial risk perspective.

Several key steps are involved if health endpoints are initiating community concerns which may lead to a cumulative risk assessment. An initial step is a thorough review of the expected etiology of the health endpoint(s) and identification of known risk factors is necessary at an early stage. Epidemiologic studies of varying degrees of complexity can be conducted depending on the nature of the identified initiating factor data. A preliminary analysis of the health endpoint (e.g., identified by a disease cluster) may include an assessment of the potential magnitude of the problem. This includes identification of the population at risk and delineation of geographic and temporal boundaries for disease ascertainment. Complete case ascertainment is another critical step in determining the magnitude of a potential disease cluster. Although a preliminary assessment of identified cases may include those identified by the community (e.g., through self-report), clinical confirmation of case diagnosis (e.g., medical chart review or diagnostic confirmation by physicians) will be needed. Diagnostic or pathologic verification will help distinguish whether the reported cases were in fact truly similar etiologically and should be considered as part of a disease cluster. This preliminary assessment also includes an examination of population characteristics of identified cases in order to determine if the disease incidence varies among any susceptible populations (e.g., children).

Once baseline levels of disease occurrence are determined, statistical analyses are conducted to determine if geographic or temporal excesses of disease are occurring. This may include use of existing environmental monitoring or public health surveillance data. Expected rates of disease can be compared to observed levels in a community to determine if disease rates are in excess. Comparisons of disease occurrence (or measures of mortality) can be made between the population residing in the area of concern and populations in other geographic areas. Temporal trends in disease incidence can also be examined in a community using time-series analyses if longitudinal health data are available. If the initial assessment determines that elevated risks are occurring in the population of concern, then additional epidemiologic studies can be conducted to further determine whether or not specific exposures are linked to the health endpoints of concern. Descriptive epidemiologic studies (e.g., an ecological study) using population-level data could help examine whether disease occurrence rates over time can be compared to existing exposure occurrence data. Analytical

epidemiologic studies using individual-level data to test specific etiologic hypotheses could include retrospective studies using existing exposure data or, alternatively, prospective studies involving collection of additional environmental samples, confounder data and biomarker data.

In keeping with best statistical practices, statistical analyses often take into consideration the likelihood that type I and type II errors result in the presence or lack of an association between disease and the exposures or stressors being examined. Considerable caution is advisable in most instances of rare disease clusters, since statistical power may be inadequate for cluster identification. The ability to infer causality of elevated disease rates to specific exposures is often limited in epidemiologic investigations of clusters. Although epidemiologic studies can be conducted to address health illness and other initiating factors of cumulative risk assessments, the utility of using epidemiologic data to draw causal inferences is beyond the scope of this report. Determining causality for specific exposures generally includes weight of evidence considerations across all existing epidemiologic and toxicological studies. Effective risk communication is also critical throughout the investigation and assessment processes in order to keep the public and stakeholders informed of the status of ongoing investigations, including the study objectives, expectations and limitations of the data and analyses. This is especially important if prospective studies are later conducted as a result of initial assessments and may help bridge differences in perception of risk between the public and risk assessors and other investigators.

2.6. LINKING THE LIST OF RELEVANT CHEMICALS TO THE POPULATION PROFILE THROUGH A CONCEPTUAL MODEL

Following the development of population profiles and the initial data collection activities, the relevant chemicals and endpoints of concern may be evaluated for linkages to sensitive population subgroups in the community or the population being assessed. In addition to identifying and examining chemical releases from local sources, the cumulative risk assessment could include an examination of possible regional and national sources of these potentially hazardous chemicals. The assessment could also include an evaluation of any unique exposure sources or pathways for the sensitive populations and an examination of the spatial relationships 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 exposed. Other community-based methods highlight the importance of community involvement in the risk assessment planning process (U.S. EPA, 1997a, 1998a).

One of the desired outputs from the Planning and Scoping phase of cumulative risk assessment (U.S. EPA, 2003a) is a conceptual model. Conceptual models provide both a written and visual representation of the structure and dynamics of the system (e.g., the community or physical site) being assessed that can be 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. Conceptual models identify which 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, the exposure and dose-response analysts jointly develop a preliminary conceptual model 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).

Figure 2-2 illustrates some key elements of a conceptual model for evaluating cumulative exposures and shows the complexity of the exposure scenario. From left to right, Figure 2-2 begins with the initial focus on the health of the population and the identification of vulnerabilities that influences the collection of appropriate exposure and dose-response data. From bottom to top, the figure shows the factors that influence cumulative risk assessments that are associated with vulnerability and multiple chemicals, exposures and routes. From right to left, Figure 2-2, depicts the typical flow of information for developing a risk assessment, depicting sources, processes, receptors and flows between them.

Conceptual models for cumulative risk cannot present all the complexities that are involved, especially those dealing with physical and toxicological interactions. Consideration of all combinations and their potential interactions can be conceptually difficult and impractical to present, so it is useful to first prioritize the potential combinations of chemicals, routes, effects. 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 2-3. 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, toxicological interactions could be screened based on toxicological significance, as indicated by the relative importance of each chemical's environmental concentration

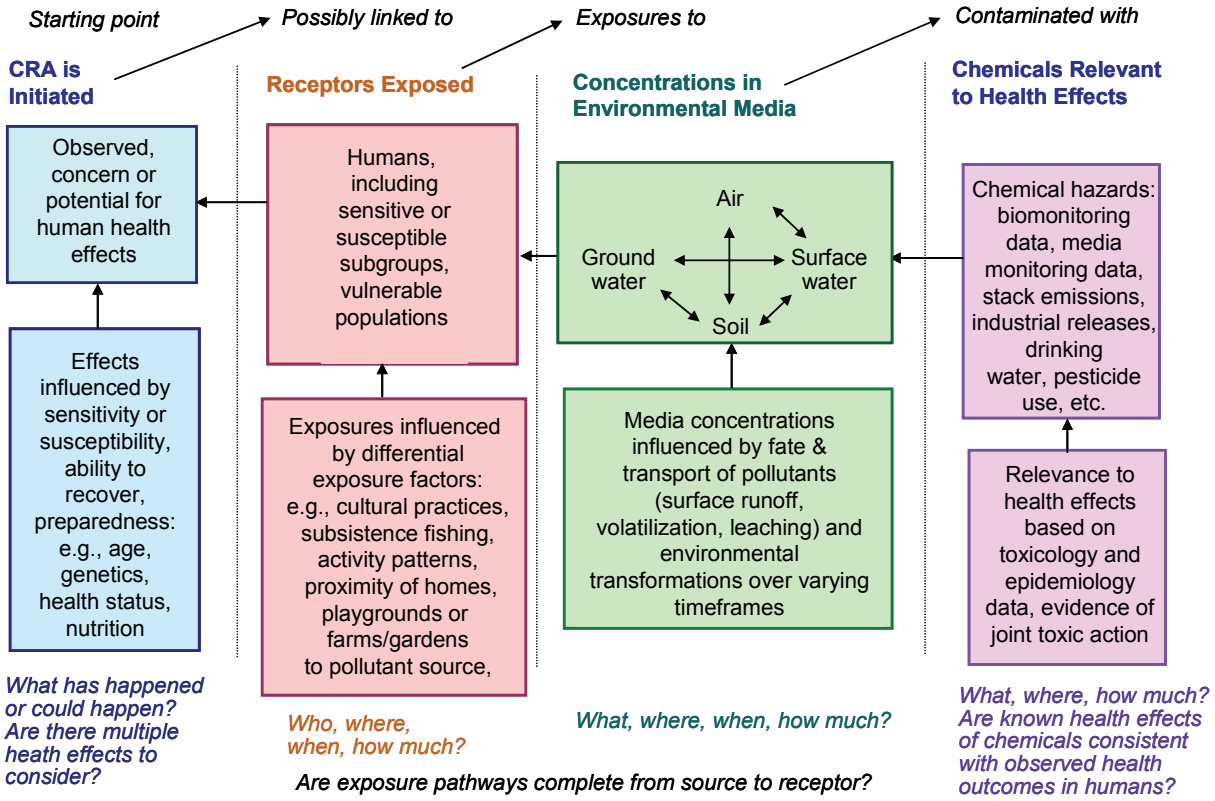


FIGURE 2-2
Conceptual Models for All Initiating Factors

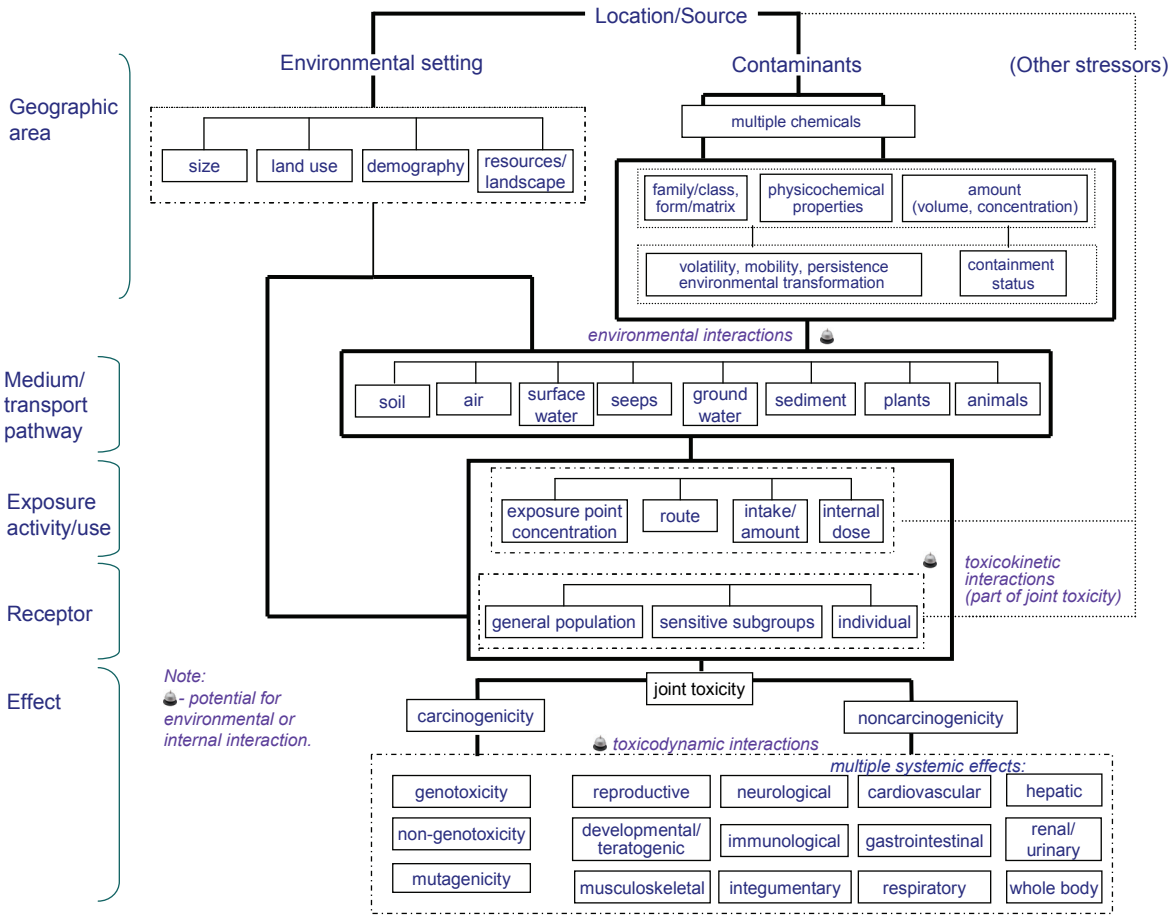


FIGURE 2-3

Example Second-Tier Detail of the Analytical Approach for Health Risk

using screening values such as the HQ. Schematic diagrams and decision flowcharts for joint toxicity and toxicological interactions are given in Figures 4-6a, b, c and d. Once that initial screening or grouping is completed, a revised conceptual model could be created, followed by more detailed analysis of the toxicological interactions such as is described in Chapter 4.

For cumulative risk assessments that encompass multiple exposure scenarios (e.g., sources, chemicals, pathways, effects), such as at a contaminated site, it is preferable to develop a hierarchy of conceptual models instead of trying to represent the multiples in one model (Suter, 1999). As described in the EPA *Risk Assessment Guidance for Superfund* (U.S. EPA, 1989a) and from a cumulative exposure assessment perspective, unique exposures in populations living near a site might require a 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. More detailed conceptual models and diagrams for cumulative exposure are presented in Chapter 3 (e.g., Figures 3-5, 3-9, 3-11, 3-12) that suggest specific processes to be evaluated.

3. EXPOSURE ASSESSMENT OF MULTIPLE CHEMICALS, EXPOSURES AND EFFECTS

This chapter provides detailed information on the exposure assessment of multiple chemicals, exposures and effects, a subset of cumulative risk issues that are described in Chapters 1 and 2. Chapters 1 and 2 of this document address several important cumulative exposure assessment concepts including a discussion of the initiating factor, the identification the exposed population and the development of a conceptual model for a cumulative risk assessment. Chapter 3 highlights existing data, methods and approaches that can be used to address cumulative exposure assessment issues that are posed as questions in Text Box 3-1. These methods can be used to determine if individuals are co-exposed to multiple pollutants and over which time periods these co-exposures occur. In collaboration with the toxicity analyst, the exposure analyst can evaluate whether the co-exposures occur over toxicologically relevant time periods and at high enough doses to be of toxicological concern. Section 3.1 defines cumulative exposure assessment as conducted in this chapter. Section 3.2 provides an overview of some exposure assessment documents that describe current EPA practice. Section 3.3 discusses approaches for conducting of a population-focused cumulative exposure assessment, giving a brief overview of the basic steps an analyst undertakes in an 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 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. Retrospective studies are discussed in Section 3.5. Section 3.6 summarizes the information in this chapter.

Cumulative Exposure Assessment Questions
(Text Box 3-1)

How are people exposed to multiple chemicals?

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

What are the intensity and duration of these exposures?

Are there uniquely susceptible or vulnerable subpopulations?

3.1. DEFINING EXPOSURE ASSESSMENT FOR CUMULATIVE RISK ASSESSMENTS THAT EVALUATE MULTIPLE CHEMICAL EXPOSURES

In cumulative risk assessments that examine risks posed by multiple chemicals, exposure assessments evaluate a population's chemical exposures through multiple

routes of exposure over time. Such assessments may encompass multiple exposure timeframes in which the timing and intensity of exposures to different chemicals are examined relative to each other. The analysts seek to determine whether the exposures to multiple chemicals can lead to toxicokinetic interactions[1] or toxicodynamic interactions[2]. In addition to providing information about multiple chemical exposures in the general population, these exposure assessments identify potentially susceptible or vulnerable subpopulations[3] in the study area and potentially unique pathways of exposure in those subpopulations.

Cumulative exposure assessments will likely rely on environmental monitoring data and environmental fate models. The community's boundary may define the geographic region of study for a cumulative exposure assessment, unlike chemical-focused assessments or single source-focused assessments. If the timing of different chemical exposures is important, the analyst can use fate models 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 either close to or distant from the population of concern. The environmental fate information needed for a such an 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 chemical transport through soils is enhanced).

While approaches to exposure assessment modeling are stressed in this chapter, the use of biomonitoring data (e.g., biomarkers of exposure) holds a great deal of promise for future cumulative risk assessments. The use of biomarkers in cumulative risk assessments currently is limited. They can provide key quantitative exposure estimates in cumulative risk assessments (e.g., biomarker data are used to estimate

[1] Toxicokinetic interactions refer to alterations in the absorption, distribution, metabolism or elimination of a toxic chemical. For example, these interactions can be mediated by the induction or inhibition of enzymes involved in xenobiotic activation or detoxification. See Appendix C U.S. EPA (2000a) for complete discussion.

[2] Toxicodynamic interactions encompass all interactions that do not directly affect absorption, distribution, metabolism or elimination of a toxic chemical. Toxicodynamic interactions affect a tissue's response or susceptibility to chemically-mediated toxic injury. Modes of toxicodynamic interactions include, among others, depletion or induction of protective factors, alterations in tissue repair, changes in hemodynamics and immunomodulation. See Appendix C U.S. EPA (2000a) for complete discussion.

[3] Vulnerable or susceptible populations in the study area can be identified during either the exposure or dose-response assessment phases of a cumulative risk assessment. This identification is based on properties of the chemicals being evaluated as well as social, cultural or genetic factors that influence vulnerability or susceptibility.

current chemical exposure levels in an affected population or the general population). Such data also can be used to verify selected exposure model results (e.g., show that specific chemical exposures and absorption are occurring in the population or, if the data are collected in a different location or under different conditions, provide evidence showing that human absorption of the chemical from environmental exposures are possible). For example, some studies have used existing blood chemical or urine chemical concentration data, such as data published in NHANES (NCHS, 2002).

Exclusive use of biomarker data in cumulative exposure assessment efforts is currently not practicable when considering a large number of diverse chemicals due to analytical and resource limitations. Analytical limitations include considerations such as whether sensitive biomarkers for many types of environmental chemicals have been developed and whether the chemical's biological half-life after absorption is sufficient to estimate exposure over a relevant exposure period. Collection of human biomarker data can be invasive and costly, resource limitations may constrain the ability of researchers to collect such data.

If collected, the interpretation of biomonitoring data and application to risk assessment can be challenging. While biomonitoring identifies individuals who are exposed and have measured internal doses reflecting absorption of a chemical, to estimate the individuals' actual exposures, the biomonitoring data would need to be integrated with additional information (e.g., exposure modeling information) to identify the pathways, timing and routes of exposure. Additional exposure and environmental modeling would be needed to identify sources of chemicals in the contaminated media. Although the use of biomonitoring data holds great promise for cumulative risk assessments, few methods exist at this time for such applications (U.S. EPA, 2003a).

When conducting cumulative risk assessments, the analyst may identify and, in some situations, wish to quantify the uncertainties associated with exposure estimates. Identifying the uncertainties in the exposure assessment is critical to a cumulative risk assessment, because limitations and uncertainties in the exposure assessment need to be highlighted in the risk characterization.

When possible, the analyst may consider developing a sensitivity analysis or quantitative analysis of uncertainty for the exposure assessment. The sensitivity analysis will be used to identify key input values to the exposure model (i.e., parameters that significantly influence the exposure modeling results), highlighting important input parameters to analyze in a quantitative uncertainty analysis.

In quantitative uncertainty analyses, the uncertainty of each input parameter can be characterized through a probabilistic distribution for use in Monte Carlo simulations.

Although detailed discussion of this topic is beyond the scope of this document, many available resources provide guidance on performing probabilistic exposure and risk assessments (e.g., Cullen and Frey, 1999); these include the following EPA sources:

- *Guiding Principles for Monte Carlo Analysis* (U.S. EPA, 1997f)
- *Superfund's Process for Conducting Probabilistic Risk Assessment* (U.S. EPA, 2001e)
- *Framework for Cumulative Risk Assessment* (U.S. EPA, 2003a)

Finally, we note that using the methods described in this chapter for a large-scale cumulative exposure assessment at this time would be very resource intensive. However, the application of approaches discussed in this chapter is considered feasible for more focused cumulative analyses (e.g., for relatively small populations, small geographic areas and limited numbers of chemicals, sources and pathways). In addition, the cost and time needed to conduct a cumulative risk assessment are expected to decrease as the data, approaches and tools to support these analyses evolve, experience is gained and the analyses become more routine.

3.2. U.S. EPA EXPOSURE ASSESSMENT GUIDANCE

The general methods the EPA uses to evaluate human exposures are presented in the *Guidelines for Exposure Assessment* (U.S. EPA, 1992a). EPA 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) and U.S. EPA (1992a) provides overall guidance in this area.

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*

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, 2005b)

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

Guidance for Developing Ecological Soil Screening Levels (U.S. EPA, 2003g)

Facilities (U.S. EPA, 2005b). While these documents focus on conventional exposure assessment approaches, they also present many cumulative exposure assessment issues.

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, EPA 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 cumulative exposure issues for specific chemical classes that can be applied in other situations.

In summary, there are a number of EPA resources that describe methods and approaches that can be used to address various aspects of exposure assessments that can comprise cumulative risk assessments. Exposure models are commonly applied to help integrate data, fill gaps and focus the scope of a more detailed phase of the risk assessment process. Models can also contribute an analytic rigor to the analysis. Various models and several tools are described in subsequent sections of this chapter and several others are highlighted in Appendix A.

Prior to selecting any model, analysts may seek to understand the development and evolution of a model. Analysts also would evaluate the strengths and limitations of an exposure model to be used in a cumulative risk assessment and determine whether the model's accuracy and the conditions under which the model was developed are consistent with the goals defined during Planning and Scoping (i.e., examine the conditions for which the model was developed and determine if the use of the model in the exposure assessment will necessitate an extrapolation beyond the conditions for which the model was developed) (NRC, 2007). Verification, validation and calibration are three key elements of this model evaluation process.

Verification focuses on assuring that the model reflects the processes it aims to characterize, by evaluating the breadth, accuracy and conformance or compliance of the underlying concepts and model framework with established guidelines. This process helps answer whether the model results are logical and whether they reflect the current understanding of relationships among exposure, dose-response and risk characterization. The EPA has drafted guidance to support the evaluation of models for various applications (U.S. EPA, 2003k) as well as guidance to address issues of verification and validation (U.S. EPA, 2002j). These terms are described in the

following discussions and have also been defined to support specific program applications (see U.S. EPA, 2006a).

Validation focuses on evaluating the analytic quality and soundness of the model, documenting its scientific basis and verifying the code, comparing the output with that of other models and conducting empirical comparisons of model predictions with field study data. This process also involves ensuring that the goals identified for the model during the planning or scoping phase are met, determining the causes of any failure to meet requirements and documenting the results.

Calibration involves comparing model results with information of known accuracy and making adjustments to the model until its results lie within reasonable bounds of the accurate information. Following calibration, the model is tested with a different set of data also of known accuracy. If the model results lie within reasonable bounds of this new dataset, this indicates success and suggests that the model can provide valid predictions when applied to other independent data sets.

Complex cumulative health exposure assessments may utilize many different models. These models will always be limited since they rely on assumptions to address specific knowledge gaps or for analytic simplification. While some of the models may have undergone verification, validation and calibration, other models may not. Depending on the availability of data for development and testing, for some of these models, a model evaluation, that is an examination of whether the model provides reasonable results (often assumed to represent a lower level of assessment for model viability) may be all that is feasible given resource constraints placed on these assessments. In some studies model evaluation also can involve benchmarking against other models to assess differences among outputs compared with expectations based on experimental data, to quantify uncertainties and sensitivities and to guide refinement of model components and underlying assumptions. Note that a similar process of verification, validation and calibration also applies to the data input to these models (U.S. EPA, 2002j). Models that have been verified or validated may be given more credibility in the assessment and may be more useful than models that have not undergone validation. This likely will be the case if the conditions under which the model will be applied are similar to those under which it was developed. If a model has not undergone model evaluation, it may not be useful in a cumulative risk analysis (NRC, 2007).

Given difficulties in obtaining sufficient data for full validation of a cumulative risk model, the first step may simply be to determine whether results are reasonable based on current scientific knowledge as it continues to evolve. In addition, partial validation

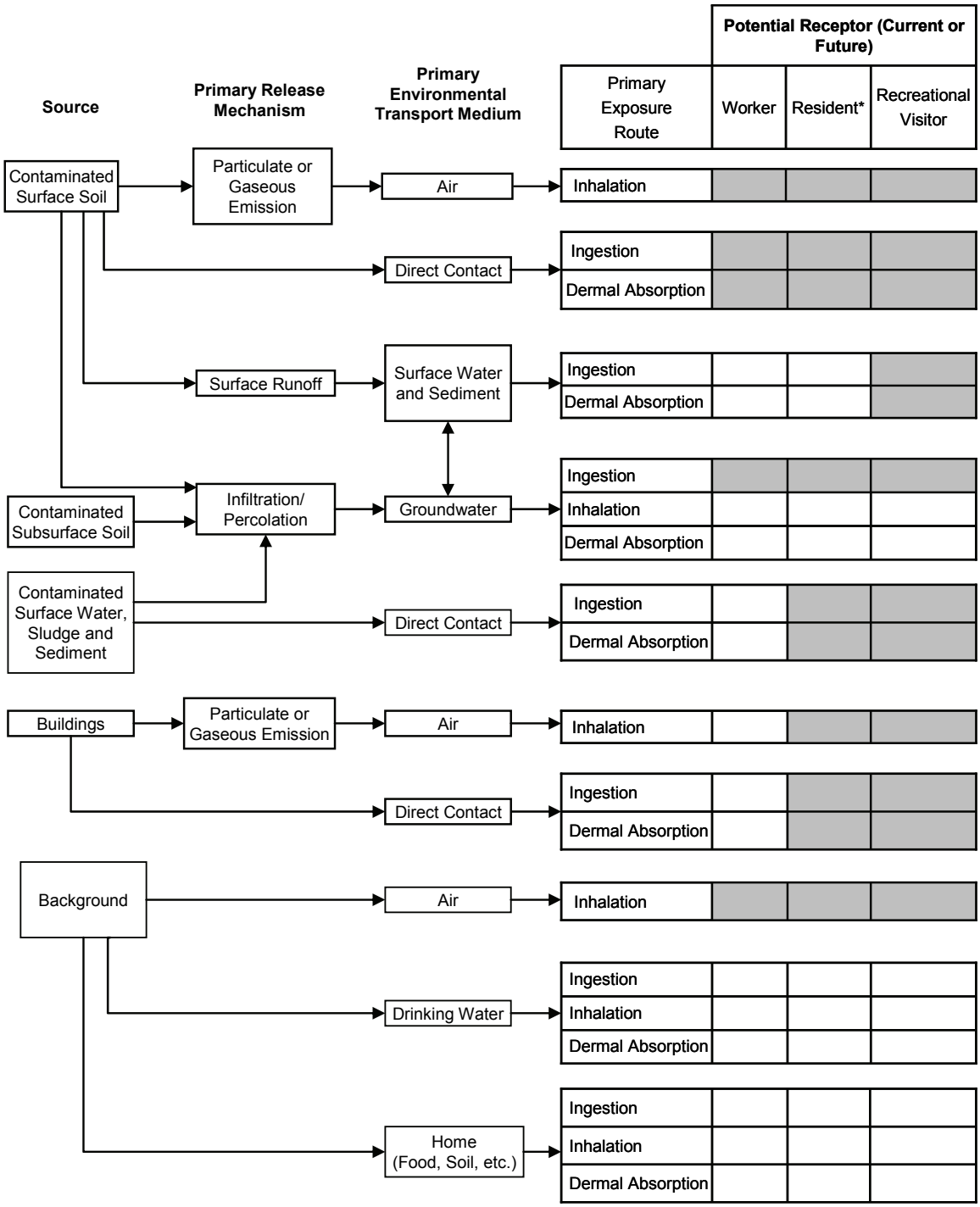
can be conducted by addressing only those components of the model for which better characterization information exists. Sensitivity analyses can help focus these efforts, targeting those elements that have the greatest impact on the model outputs. Comparing these models with other models that frame the cumulative risk question from different perspectives (e.g., those that emphasize different elements) also can strengthen the modeling process.

As an example of progressive model validation, many years ago the dioxin data from the Seveso plume were combined with health effects data from the local community in order to reconstruct doses and improve the extant scientific model of human toxicity. Early conceptual models have since been updated with human data, including those from recent individual exposure incidents (CNN, 2004; Edmond et al., 2005; also see model development description in NRC, 2007). Thus, model representation of human exposure, toxicity and risk continues to be refined as new data become available.

3.3. CUMULATIVE EXPOSURE ASSESSMENT: ANALYSIS PHASE

As described in U.S. EPA risk assessment guidance documents, the analytic phase of an exposure assessment begins after the analyst has developed a preliminary list of chemicals of potential concern and has identified the population and subpopulations of concern. The materials presented in Chapter 2 identify data sources and approaches that can be considered when conducting a cumulative exposure. The applicable procedures differ depending on the initiating factor. If the initiating factor is *sources*, typically there will be a well characterized list of chemicals known to be released from the identified sources under both typical and abnormal operating conditions. If the initiating factor is *chemical concentrations* then the initial list of relevent chemicals will be identified during the characterization of the initiating factor. In a cumulative risk assessment, the exposure analyst will typically consult with the toxicity analyst to determine if other chemicals need to be considered for inclusion in the analysis because compounds of concern are known to interact toxicologically with the chemicals that initiated the cumulative risk assessment. If the initiating factor is *population illness*, the toxicity and exposure analysts will colaborate closely to identify the types of chemical exposures that could be associated with the illness and to determine if such exposures could occur within the population (e.g., given the emission sources in the area or past land uses).

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



* 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

model for a contaminated site. Although the initiating factors could vary across communities, as indicated in Figure 2-1, the same exposure assessment steps are addressed (see Text Box 3-3). In each of Sections 3.3.1, 3.3.2 and 3.3.3, 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 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 were, 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 risk 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. The analyst routinely assembles geographic and meteorologic data when conducting an exposure assessment. Basic geographic information about a community is available through a variety of sources including those offered by the U.S. Geological Service and U.S. Department of Agriculture. Climate and meteorologic data are available from the National Oceanic and Atmospheric Administration, e.g., the National Weather Service. Analysts also identify land uses. Land use analyses include the identification of all residential areas, work places, recreational areas and places where foods are grown or collected as well as relevant pollution sources inside and outside the community. For example, regional—or outside—emission sources could impact pollutant levels in the community and in some analyses these require identification. 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. Past uses may provide the analyst with important insights in to once-common polluting practices and to potential past exposures.

In a community assessment, in addition to examining the contaminants present, the analyst may 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, the EPA requires that the assessment include an examination of the concentrations in the local environment from these atmospheric sources and the potential for airborne contamination from the Superfund site (U.S. EPA, 1989a). Ambient data for such an analysis can be obtained from various organizations, such as U.S. EPA regional offices and state, county or city environmental agencies. Pollutant release data can be obtained from the Toxics Release Inventory, http://www.epa.gov/tri/chemical/index.htm#chemlist; Appendix A lists additional resources providing such data.

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 dioxin document (2003c) lists typical concentrations of dioxin congeners in the U.S. food supply. These nationally representative samples could be incorporated into a cumulative exposure assessment, if relevant. Such exposure pathways when combined with local exposure pathways may 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 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 WOE 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 location of sites where people in a community could be exposed. Community members may provide valuable input into the identification of such sites, the relevant activities that may occur there and the frequency with which the site is or may have been used. This information can provide insights into potential exposures and potential subpopulations being exposed through use of the location. When performing cumulative exposure assessments, the analyst may need to evaluate exposures where community members gather. For example, community members gather in schools and at playgrounds, and the analyst may need to evaluate exposures in susceptible populations (e.g., asthmatic children) at these locations. The analyst also may want to examine exposures that occur in and around facilities that care for the elderly and disabled members of a community. Depending on the chemicals being evaluated, the exposure and toxicity analysts may wish to colaborate closely to identify other settings where chemical exposures could occur in vulnerable populations (see Section 3.3.1.2 for further discussion).

3.3.1.2. Receptor Characteristics Considered in Cumulative Risk Assessments — During characterization of the exposure setting, the analyst identifies individuals and population groups that could be exposed to contaminants. Then, information on the residential locations, activity patterns and workplaces is collected.

Cumulative risk assessments also examine exposures among both "typical" members of a community and vulnerable populations. Usually, the exposure analyst and the toxicity analyst work together to identify the potentially vulnerable populations. U.S. EPA's *Framework for Cumulative Risk* (2003a) adopts "vulnerability" concepts described by Kasperson that encompass the topic of receptor characteristics. The EPA document details four areas of vulnerability:

- Differential exposure
- Susceptibility/sensitivity
- Differential preparedness
- 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 elevated exposures to pollutants (e.g., subsistence fishing). 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. The analyst may conduct community-specific surveys to fill important gaps (U.S. EPA, 1998a). The analyst also may meet with specific groups that are or could be affected, in order 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 risk 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 risk assessment may include diverse factors such as genetic susceptibility, age, stress, disease state, economic status, ethnicity, health status, availability of health care, etc (see Figure 1-6). It is particularly important that the analyst evaluate whether certain potentially susceptible populations are exposed to high levels of pollutants. Examples of information the analyst can use to support this evaluation are highlighted in Text Box 3-5. Pregnant women can represent a subgroup of special concern due to the fetus's sensitivity for potential effects under some types of chemical exposures. For example, the fetal nervous system is considered the most sensitive target of methylmercury and the 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 registry

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 and not yet fully protective. 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 EPA 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.

Other people with higher than average biological sensitivity to environmental stressors include those with allergies and with pre-existing medical conditions (e.g., asthma). Some state health departments have established health registries for health conditions, such as asthma, and for exposure measurements, such as blood lead levels. The analyst also may contact these agencies 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 Handbook* (U.S. EPA, 1997c) provides factors associated with these receptors (e.g., quantities of homegrown vegetables consumed daily).

In typical assessments, the individual receptors are located in close proximity to a pollution source (e.g., at the fence line, the nearest housing development or the closest fishable lake). The analysts may have to use atmospheric dispersion models to identify sites proximal to multiple pollution sources. The analyst 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), 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. The exposure analyst also evaluates exposures in vulnerable populations (Section 3.3.1.2). If these screening practices do not reveal exposures of concern, the exposure analyst can drop the receptors from the analysis, after consultation with the dose-response analyst.

If the exposure levels are deemed to be of concern, then the analyst can use demographic data to estimate the typical ages and ethnicities 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* describes how chemicals are transported from a source to a person or subpopulation. *An exposure route* identifies the way the contaminant actually enters the body. For environmental pollutants, the major exposure routes are inhalation, ingestion and dermal absorption. This section identifies considerations for how exposure pathways can be evaluated in an assessment. The basic process elements are summarized in Text Box 3-6.

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)

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 risk 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 risk assessment issues can be considered. If the initiating factor is population illness, then the exposure analyst would have to collaborate with the toxicity analyst to identify possible relevant chemicals and then determine if there are possible sources of such contaminants in the local environment. If the initiating factor is elevated chemical concentrations or multiple sources, then the sequence of steps is similar to that which follows.

3.3.2.1. Sources and Fates of Chemicals and Chemical Mixtures — When performing a cumulative risk assessment initiated by environmental contaminants, the analyst would want to identify all sources being considered and all potential exposure pathways for each medium of exposure. The analyst then reviews the pathways to determine if they are relevant. The completeness of each exposure pathway is then evaluated. 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
- A route of exposure at that point

The exposure analyst develops criteria for inclusion in the cumulative risk assessment after discussion with the toxicity analyst; then 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 risk assessment.

In cumulative exposure assessment, 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.

For example, BIOCHLOR is a numerical screening model developed by the Air Force and maintained by the EPA to assess monitored natural attenuation (MNA) for sites contaminated with chlorinated solvents. The code simulates solute transport for sequential reactions from a single parent chemical, involving up to four fate products (Jones et al., 2006). It can be run either with or without biotransformation assuming sequential first-order decay (notably for reductive dechlorination, which is generally the main biodegradation process at these sites). The model has been applied for a number of projects to integrate site-specific information into evaluations of solvent degradation. These projects extend beyond industrial Superfund sites (Clement et al., 2002) and U.S. federal sites (U.S. DOE, 2005) to international sites (Nakashima et al., 2005), with a variety of case studies reviewed by McGuire et al. (2004). Where site-specific data are unavailable, the User's Manual provides ranges for a number of input parameters (available from U.S. EPA, 2002k), which can be used to help focus site investigations in support of MNA suitability or performance assessments as indicated.

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 (VOC) 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 environmental fate of multiple pollutants and cumulative exposures.

When evaluating environmental fate and transport across media for these assessments, it is important[4] that mass 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.

When evaluating contaminant fate, it is important to consider setting conditions that can contribute to chemical-chemical interactions. This applies to natural systems such as fields or ponds as well as manmade systems such as drinking water distribution networks, where chemical interactions (often combined with microbial processes) can convert introduced compounds to other forms. Main environmental reaction processes are oxidation, complex formation with various ligands and biologically mediated reduction (methylation).

The environmental fate of mercury (Hg) illustrates the importance of considering setting conditions. Hg could be released from a combustor as an elemental vapor and converted in the local atmosphere to a reactive gaseous form. Reactive gaseous Hg is thought to deposit rapidly to the surface of the earth. In aqueous environments and in wetlands, mercury can be transformed to methylmercury, which bioaccumulates in fish. Setting conditions, including wind direction; wind speed; local atmospheric chemistry; proximity of Hg releases to wetlands, lakes or rivers; the aquatic chemistry in these local bodies of water; and the size of the watershed, influence methylmercury levels in local fish.

[4] Although models may not explicitly conserve mass, post-processing can be applied to assure that this is maintained.

TABLE 3-1

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

Chemical	Key Degradation Products	General Fate/ Persistence	Environmental Half-Life and Reaction Mechanism		Log Kow (unitless)	Log Koc (unitless)	Illustrative U.S. Concentration	EPA IRIS Toxicity Value	Toxicity Relative to Parent
Pesticides									
Aldrin	*(see below)*	Binds tightly to soil and does not leach readily, so is not usually found in groundwater; moderately persistent; bioaccumulates	Air 36 minutes (Howard, 1989)	*Hydroxyl radical oxidation*	6.5 (5.7-7.4) (bioaccumulation likely) (Howard, 1989, ATSDR, 2002a)	7.7 (5.4-7.7) (expected to strongly adhere to soil) (ATSDR, 2002a)	Air 0.00003 ppb (mean for 1970-72 from 13.5% positive samples, 16 states) Water 0.001 ppb (STORET median, ambient water, 40% detects; 1985) Sediment 0.1 ppb (STORET median, 33% detects; 1985) (ATSDR, 2002a)	RfD 0.00003 mg/kg-d DWUR: 0.49 per mg/L IUR: 4.9 per mg/m^3	NA
			Water 5 weeks (Howard, 1989)	*(not specified)*					
			Soil: 20-109 days (ATSDR, 2002a; Howard, 1989)	*(not specified)*					
	Dieldrin	As for aldrin, but very persistent	Air *not specified* (Howard, 1989)	*Photo-degradation*	6.2 (4.3-6.2) (bioaccumulation likely) (ATSDR, 2002a)	6.7 (expected to strongly adhere to soil) (ATSDR, 2002a)	Air 0.0001 ppb (mean for 1970-72 from 94% positive samples, 16 states) Water 0.001 ppb (STORET median, ambient water, 40% detects; 1985) Soil 1-49 ppb (mean) Sediment 0.8 ppb (STORET median, 33% detects; 1985) (ATSDR, 2002a)	RfD 0.00005 mg/kg-d DWUR 0.46 per mg/L IUR 4.6 per mg/m^3	Noncancer (oral) 60% Cancer (oral-inhln) 94%
			Water: hours to months (Howard, 1989)	*Evaporation*					
			Soil 2.5-7 years (ATSDR, 2002a; Howard, 1989)	*(not specified)*					

TABLE 3-1 cont.

Chemical	Key Degradation Products	General Fate/ Persistence	Environmental Half-Life and Reaction Mechanism		Log Kow (unitless)	Log Koc (unitless)	Illustrative U.S. Concentration	EPA IRIS Toxicity Value	Toxicity Relative to Parent
Chlordane	NA (this compound is not typically transformed in the environment)	As for dieldrin, and in surface water will volatilize and adsorb to sediments	Air 1.3 days (ATSDR, 1994a)	*(not specified)*	5.5 (estimate for pure chemical) (bioaccumulation likely) (U.S. EPA, 2006b; ATSDR 1994a; Howard, 1989)	3.5-4.6 (4.2 -4.4 estimated) 4.1 (mean) expected to adhere to soil) (U.S. EPA, 1996a, 2006b; ATSDR, 1994a)	Surface and groundwater 0.1 ppb (mean in selected areas) Soil <1-140 ppm (ATSDR, 1994a)	RfD 0.0005 mg/kg-d RfC 0.7 µg/m^3 DWUR 0.01 per mg/L IUR 0.1 per mg/m^3	NA
			6.2 hours (Howard, 1989)	*Hydroxyl radical oxidation*					
			Water 240 days (U.S. EPA, 2000b)	*(not specified)*					
			7.3-7.9 hours (Howard, 1989)	*Volatilization*					
			Soil 3.3 years (Howard, 1989)	*(not specified)*					

TABLE 3-1 cont.

Chemical	Key Degradation Products	General Fate/ Persistence	Environmental Half-Life and Reaction Mechanism		Log Kow (unitless)	Log Koc (unitless)	Illustrative U.S. Concentration	EPA IRIS Toxicity Value	Toxicity Relative to Parent
Solvents									
Carbon tetrachloride	*(see below)*	Stable in air; volatilizes rapidly from soil and surface water; little binds to soil (moderately soluble so can leach to groundwater); does not bioaccumulate	Air 330 years	*Oxidation*	2.6-2.8 (ATSDR, 2003a; Howard, 1989)	2.0 (expected to move with groundwater) (ATSDR, 2003a)	Air 0.2 ppb (mean) Drinking water 0.5 ppb (mean for the 3% of samples with detectable levels) (ATSDR, 2003a)	RfD 0.0007 mg/kg-d DWUR 0.0037 per mg/L IUR 0.015 per mg/m^3	NA
			Groundwater: 0.4-4.5 days	*Reaction with minerals*					
			Surface water: 0.5-1 years	*Aerobic biodegradation*					
			7-28 days	*Anaerobic biodegradation*					
			7000 years	*Hydrolysis*					
			Soil 0.5-1 years *(data from ATSDR 2003a)*	*(Based on aerobic conditions)*					
	Chloroform	Persistent in groundwater; does not bioaccumulate	Air 80 days (Howard, 1989)	*Hydroxyl radical oxidation*	2.0 (not likely to bioaccumulate) (ATSDR, 1997a; Howard, 1989)	2.0 (mean) (expected to move with groundwater) (ATSDR, 1997a)	Drinking water: 23 ppb (mean) (ATSDR, 2003a)	RfD 0.01 mg/kg-d IUR 0.023 per mg/m^3	Noncancer (oral) 7% Cancer, (inhaln) 150%
			Water 36-40 hours (Howard, 1989)	*Volatilization*					
			Surface water 44 days (ATSDR, 1997a)	*Hydrated electrons*					

TABLE 3-1 cont.

Chemical	Key Degradation Products	General Fate/ Persistence	Environmental Half-Life and Reaction Mechanism		Log Kow (unitless)	Log Koc (unitless)	Illustrative U.S. Concentration	EPA IRIS Toxicity Value	Toxicity Relative to Parent
	Chlorine	Reacts with water to form hypochlorous and hydrochloric acids; volatilizes from soil; persists in groundwater; does not bioaccumulate	Air seconds to minutes (NPI, 2005) Surface water seconds to minutes (U.S. EPA, 1994b)	*Hydrolysis*	0.9 (not likely to bioaccumulate) (TCEQ, 2003)	Not identified (organic carbon in soil does not appear to play a major role)	Air 0.0006-0.02 ppm (HSDB, 1991; ARB, 1997) Drinking water 0.2-1 mg/L (WHO, 1996) 1.4-2.7 mg/L (finished water in several U.S. cities) (U.S. EPA, 1981)	RfD 0.1 mg/kg-d	Noncancer (oral): 0.7%
Tetrachloro-ethylene	*(see below)*	Volatilizes rapidly from surface water and soil; can leach slowly to groundwater, (only slow soil biodegradation); does not bioaccumulate	Air 70-250 days (ATSDR, 1997b)	*Hydroxyl radical oxidation*	2.5-3.4 (not likely to bioaccumulate) (ATSDR, 1997b; Mackay et al., 2006, Howard, 1989)	1.8-3.6 (expected to moderately bind to soil and can leach to groundwater) (ATSDR, 1997b; Mackay et al., 2006)	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) (ATSDR, 1997b)	RfD 0.01 mg/kg-d	NA
			110 days (Mackay et al., 2006)	*Tropospheric reaction*					
			Water 0.8-6 years (ATSDR, 1997b)	*Hydrolysis*					
			4-4.5 hours (ATSDR, 1997b)	*Volatilization*					
			180 days (TOXNET, 2005)	*Aerobic biodegradation*					
			98 days (HSDB, 2006)	*Anaerobic biodegradation*					
			Soil 2-16 days (ATSDR, 1997b; Mackey et al., 2006)	*Volatilization*					

TABLE 3-1 cont.

Chemical	Key Degradation Products	General Fate/ Persistence	Environmental Half-Life and Reaction Mechanism		Log Kow (unitless)	Log Koc (unitless)	Illustrative U.S. Concentration	EPA IRIS Toxicity Value	Toxicity Relative to Parent
Tetrachloro-ethylene (cont.)	Trichloro-ethylene	Volatilizes quickly from surface water; binds to soil; persistent in groundwater; does not bioaccumulate	Air 6.8 days (ATSDR, 1997c)	*Hydroxyl radical oxidation*	2.3-2.6 (not likely to bioaccumulate) (ATSDR, 1997c; Howard, 1989; Mackay et al., 2006)	2.0-2.7 expected to moderately bind to soil and move with groundwater) (ATSDR, 1997c; Howard, 1989; Mackay et al., 2006)	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) (ATSDR, 1997c)	NA	NA
			Water 100 days (Mackay et al., 2006)	*Aerobic biodegradation*					
			400 days (Mackay et al., 2006)	*Anaerobic biodegradation*					
			320 days (Mackay et al., 2006)	*Hydrolysis*					
			Months to millions of years (ATSDR, 1997c)	*Hydrolysis*					
	1,1-Dichloro-ethylene	Volatilizes relatively quickly from surface water and soil; moves with groundwater; stable in water; degradation expected to be slow; does not bioaccumulate (U.S. EPA, 2006c)	Air 2.3 days (ATSDR, 1994b; Mackay et al., 2006)	*Hydroxyl radical oxidation*	1.3-2.1 (not likely to bioaccumulate) (ATSDR, 1994b; Mackay et al., 2006)	1.8-2.2 (not expected to bind to soil; expected to move with groundwater) (ATSDR, 1994b; Mackay et al., 2006)	Air 4.6 ppb (mean); Drinking water 0.6 ppb (mean, for the 3% of samples with detectable levels) (ATSDR, 1994b)	RfD: 0.05 mg/kg-d RfC: 0.2 mg/m^3	Noncancer (oral): 20%
			11 hours (Mackay et al., 2006)	*Photooxidation*					
			Water 4 days (mean) (ATSDR, 1994b)	*Volatilization*					
			670-4300 hours (Mackay et al., 2006)	*Aerobic*					

TABLE 3-1 cont.

Chemical	Key Degradation Products	General Fate/ Persistence	Environmental Half-Life and Reaction Mechanism		Log Kow (unitless)	Log Koc (unitless)	Illustrative U.S. Concentration	EPA IRIS Toxicity Value	Toxicity Relative to Parent
			Soil <10 days (Mackay et al., 2006)	*(not specified)*					
	1,2-Dichloro-ethylene, trans- (the cis- form is also produced but no toxicity value exists)	Volatilizes quickly from surface water and soil; moves with groundwater; does not bioaccumulate	Air 3.5-5 days (ATSDR, 1996; Howard, 1989; Mackay et al., 2006)	*Hydroxyl radical oxidation*	2.1 (not likely to bioaccumulate) (ATSDR, 1996; Howard, 1989; Mackay et al., 2006)	1.6-1.8 (not expected to bind to soil; expected to move with groundwater) (ATSDR, 1996; Mackay et al., 2006)	Air 0.037 ppb (median) Drinking water and groundwater 173 ppb (mean) (ATSDR, 1996)	RfD 0.02 mg/kg-d	Noncancer (oral) 50%
			Surface water 3-6.2 hours (ATSDR, 1996; Howard, 1989)	*Volatilization*					
	Vinyl chloride	Volatilizes quickly from surface water and soil; moves with groundwater; does not bioaccumulate	Air 1.5 days (Howard, 1989; Mackay et al., 2006)	*Hydroxyl radical oxidation*	1.4-2.8 (not likely to bioaccumulate) (ATSDR, 1997d; Howard, 1989; Mackay et al., 2006)	0.5-2.0 (not expected to bind to soil; expected to move with groundwater) (ATSDR, 1997d; Mackay et al., 2006)	Air 0 to 0.04 ppm (generally not detected, but can be elevated near landfills or industrial facilities with this chemical or parents) Drinking water 1, 8.4 ppb (maxima for random and nonrandom sites, respectively; detected in 0.74% of groundwater supplies) (ATSDR, 1996)	RfD 0.003 mg/kg-d DWUR (from birth) 0.0021 per mg/L IUR (from birth) 0.0088 per mg/m3	Noncancer (oral) 333%
			11 weeks (Mackay et al., 2006)	*Tropospheric reactions*					
			Water 0.81 hours (Howard, 1989; Mackay et al., 2006)	*Volatilization*					
			Soil 30-180 days (Mackay et al., 2006)	*(not specified)*					

TABLE 3-1 cont.

Chemical	Key Degradation Products	General Fate/ Persistence	Environmental Half-Life and Reaction Mechanism	Log Kow (unitless)	Log Koc (unitless)	Illustrative U.S. Concentration	EPA IRIS Toxicity Value	Toxicity Relative to Parent
	Carbon tetrachloride	*As described above (for listing its as a primary chemical solvent)*					RfD 0.0007 mg/kg-d (and other toxicity values)	Noncancer (oral) 1400%

*Organic compounds illustrated here are often found at Superfund sites; others also commonly found include acetone, 2-butanone and methylene chloride; polycyclic aromatic hydrocarbons (PAHs)/naphthalene, pentachlorophenol and polychlorinated biphenyls (PCBs); and benzene, toluene and xylene (designated by U.S. EPA as "pending" for this list). (Source: U.S. EPA's *Common Chemicals Found at Superfund Sites*, http://www.epa.gov/superfund/resources/chemicals.htm.) General fate content is highlighted from the ATSDR toxicological profiles as also supported by various EPA facts sheets (as indicated), and many properties and environmental levels are also from the toxicological profiles. NA = not available. Gray shading indicates the entry is not applicable because this is the parent compound. Toxicity values are highlighted from the EPA IRIS database (U.S. EPA, 2007); the RfD (reference dose) and RfC (reference concentration) address the noncancer endpoint, while the DWUR (drinking water unit risk) and IUR (inhalation unit risk) address the cancer endpoint; inhln = inhalation.

The environmental half-life represents the time it takes for the initial amount of a chemical to be reduced by half in that medium. To streamline the presentation (with many of the values having been calculated or estimated), numbers are generally rounded to two significant figures or one decimal point. 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. As it increases above 6, the chemical is less likely to bioconcentrate, approaching no bioconcentration at a log Kow of 12. 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 values are also presented as logarithms because, like Kow, this measure 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: U.S. EPA *Pollution Prevention (P2) Framework, Environmental Fate Models*, see http://www.epa.gov/oppt/p2framework/docs/envfate.htm).

Note that these chemicals were selected to illustrate fate links for pesticides of historical interest and for solvents commonly found at contaminated sites. The level of information highlighted in this table these will typically not exist for all compounds for a given cumulative risk assessment. The unavailability of key data for one or more chemicals being assessed can represent a main source of uncertainty for the analysis, and it is important to address this as part of the risk characterization discussion.

Major ions in the environment with which introduced chemicals can react include iron and manganese cations and anions of sulfur and phosphorous anions. Naturally occurring metals such as arsenic (As), Cd, chromium (Cr), Hg, nickel (Ni), Pb and zinc (Zn) are also common, introduced contaminants in terrestrial and aquatic systems, from releases such as combustor emissions and effluent discharges. Metal cations can exist as potentially toxic uncomplexed species or as relatively nontoxic complexed forms, usually with organic ligands or non-metallic inorganic anions such as oxides, sulfates or phosphates.

The potential for chemical-chemical interactions depends on many factors related both to the chemical (e.g., for metals, the activity, solubility, electronegativity, coordination number and density) and the nature of the medium (e.g., for aquatic systems, the pH and temperature, oxidizing and photolysis potential; organic, particulate and microbial content and salinity and presence of other chemicals). To illustrate for one of these factors, the pH of natural or treated waters affects both the type of metal complexes that form and the fraction of various species that would precipitate. For example, metal carbonates are expected to precipitate as the pH rises above 8, while the cation and anion would stay in solution at an acidic pH below 6. Thus, when assessing the joint fate of contaminants to estimate exposure levels for a cumulative risk assessment, characterizing the setting well can be key to a realistic analysis.

The various chemical interactions in a drinking water distribution system also illustrate the types of interactions that analysts may encounter when conducting a cumulative risk assessment. Free chlorine (Cl_2), which can be represented by hypochlorous acid (HOCl) or hypochlorite (OCl), is a common disinfection residual. Cl_2 is a potent oxidizer that is a strongly electronegative and acts as an electron acceptor in forming complexes with a wide variety of both inorganic and organic chemicals that could be present in finished water. For example, it can combine readily with (1) ammonia, to form chloramines (2) reducing agents such as ferrous ion (Fe^{2+}), to form the chloride and (3) humic material, to form trihalomethanes. In aerobic systems, chlorine can also rapidly convert the trivalent form of As (arsenite) to the pentavalent form (arsenate), which is less toxic when based on environmental exposure levels (due to less cellular uptake than the trivalent form, while equivalent intracellular levels are equipotent; ATSDR, 2000d). Biological processes can also combine to produce organic forms of As, which are generally less toxic than inorganic forms that may have been introduced to the system. Thus, for both natural and manmade systems, a number of chemical-chemical interactions can influence the exposure profile for a cumulative risk assessment.

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). Table 3-1 shows that the half-life for tritium is approximately 12.3 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 non-radioactive chemicals reflects environmental half-life.

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. *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 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 logically would jointly discuss this issue. It can be helpful for the exposure analyst to consider three broad categories of transfers that can occur between environmental compartments:

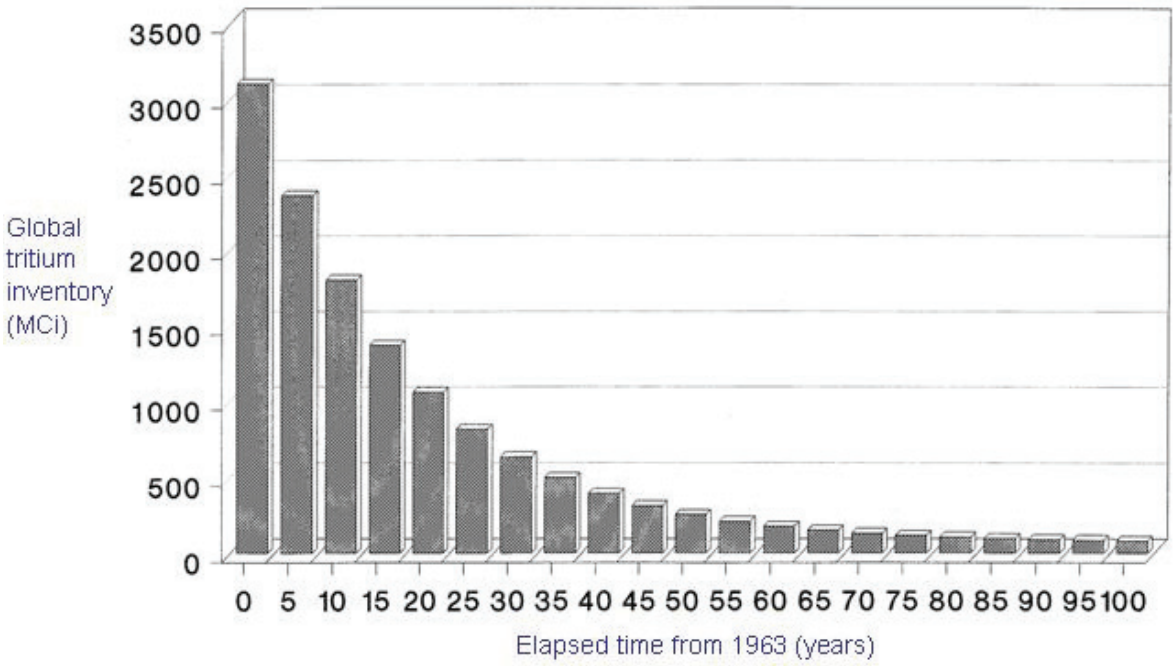


FIGURE 3-2

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

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

Mixture components can be differentially transferred between abiotic media. For example, 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 U.S. until 1982 when it was canceled for most uses. It was used primarily in the southern U.S. 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. This section provides six tables that illustrate 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 could 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.

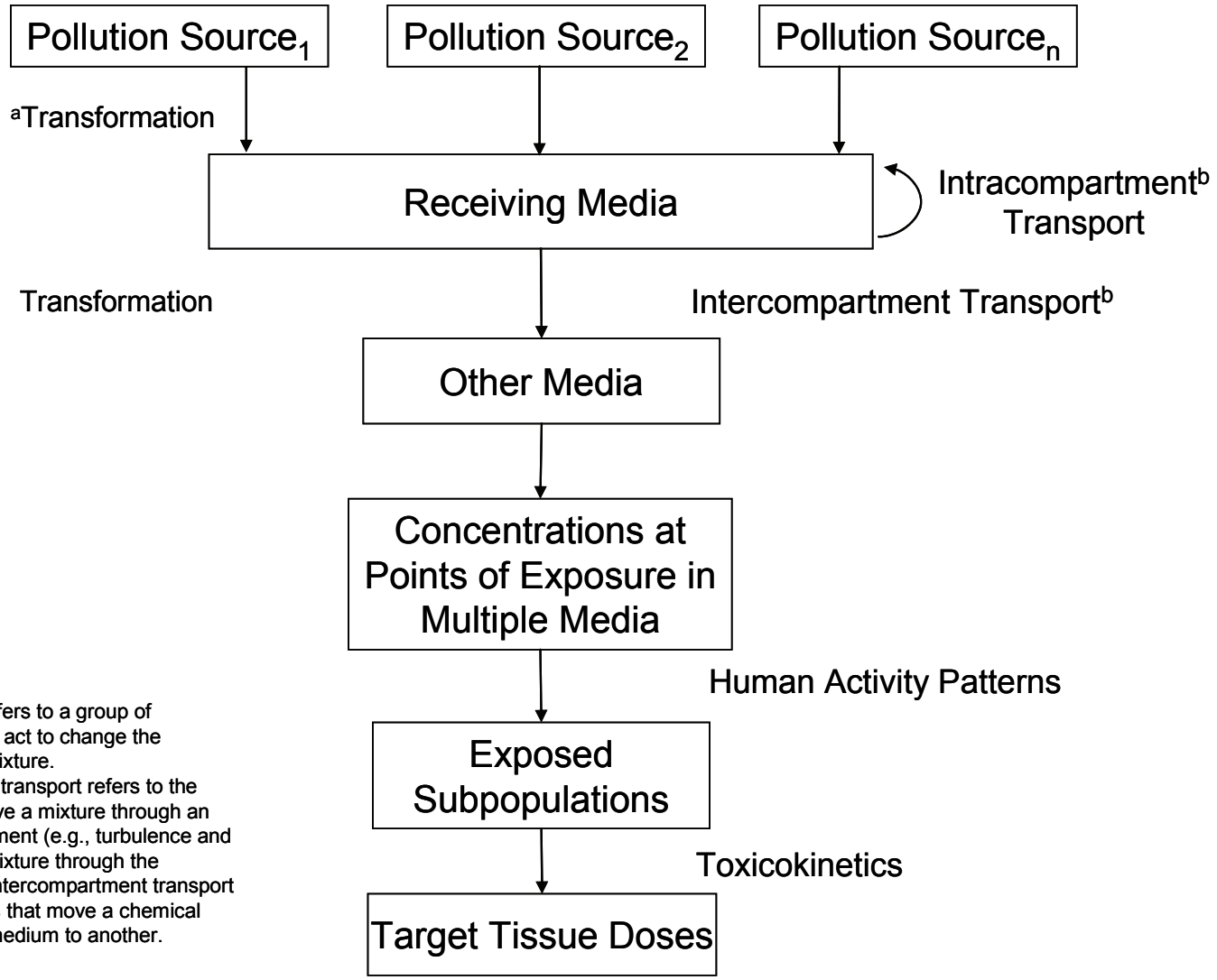
While chemicals can be easily grouped based on common sources and releases (e.g., chemicals in diesel exhaust), the usefulness of groupings for various chemical classes can be improved based on typical primary release mechanisms that would be expected to control initial contamination and migration behavior 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 (soil-water partition coefficient, 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 provide an indication of the amounts and types of sorption sites are 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.[5] The analysts may evaluate the soil type, geochemistry and other data to determine generally appropriate values and site-specific studies important to the selection of the actual values for key contaminants. This concept is illustrated in Text Box 3-7. Table 3-5 gives examples of Kow and solubility values for selected chemicals to support these types of groupings.

[5] 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.



[a]Transformation refers to a group of processes that can act to change the composition of a mixture.
[b]Intracompartment transport refers to the processes that move a mixture through an individual compartment (e.g., turbulence and wind will move a mixture through the atmosphere) and intercompartment transport refers to processes that move a chemical mixture from one medium to another.

FIGURE 3-3
Approach for Estimating Exposure in Cumulative Risk Assessments

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 (benzene, toluene, ethylbenzene, xylene), Pesticides	Cations and 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; NO_x = nitrogen oxides; and SO_2 = sulfur dioxide.

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)[c]
Organic matter in soil and sediments, soil organisms	<u>High for</u> High Kow/Kd Low biodegradability <u>Low for</u> High Kow/Kd High biodegradability	<u>Presence favored by</u> High Kow/Kd High persistence	<u>High binding for</u> High-Kow/Kd organics and inorganics <u>Low binding for</u> Low-Kow/Kd organics and inorganics
Soil inorganic phase	<u>High for</u> High-Kd inorganics Low-Ksp inorganics (including metals that form complexes in soil) <u>Low for</u> Low Kow/Kd organics/inorganics	<u>Presence favored by</u> High-Kd and low-Ksp inorganics	<u>High mobility for</u> Cations, anions, water- soluble organics (low Kow/Kd) High-Ksp colloids <u>Low mobility for</u> High-Kow/Kd organics High-Ksp solids
Surface water	<u>Higher for</u> Insoluble (high Kow) Non-photodegradable Non-biodegradable <u>Lower for</u> Water soluble (low Kow) Volatile (low K_H) Photodegradable Biodegradable	<u>Presence favored by</u> Low Kow/Kd High K_H (low volatility to air) High-Ksp inorganics	<u>High transport for</u> High solubility Low volatility <u>Low transport for</u> Precipitates (low Ksp) Low solubility (high Kow) Biodegradable Photodegradable

TABLE 3-3 cont.

Environmental Compartment	Persistence (environmental half life)	Environmental Partitioning (equilibrium-based)[b]	Mobility (convection- and dispersion-based)
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
Air	Higher for Low photodegradable Low reaction rate with hydroxyl radical and 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] 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.

[c] In general, advection is transport by large-scale motions and can be described as the movement of a chemical by virtue of its presence in a medium that is flowing. Convection describes local transport phenomena and can be described by the flux of a chemical through porous media. Diffusion is a redistribution (spreading/dilution) of a chemical mass within a phase attributable to molecular (Brownian) motion and tending toward equilibrium (e.g., movement of a chemical from an area of high concentration to one of lower concentration), which results in the net transport of a chemical within the liquid, solid or gas phase. Dispersion is net transport (mixing) resulting from differential advection, which can be referred to as turbulent diffusion causing longitudinal, transverse and vertical spreading.

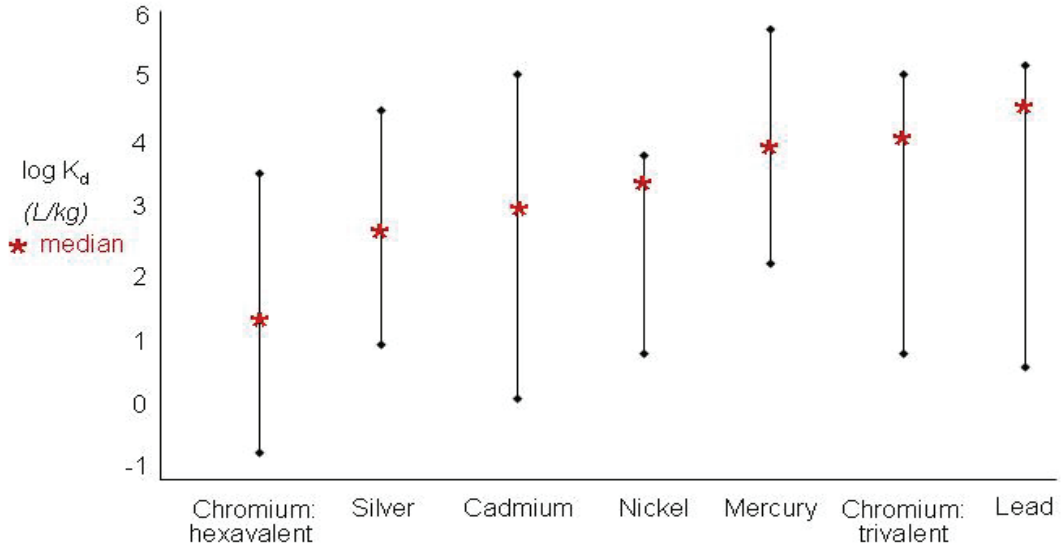


FIGURE 3-4

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

Illustration of Groupings Based on Properties and Fate
(Text Box 3-7)

Chemicals can be grouped based on expected persistence or degradation in various environmental compartments, as a general indication of potential joint exposures to various contaminated media.

For example, organic contaminants with high Kow and low volatility that would be expected to be found together in sediments and in the lipids of fish would include: persistent pesticides aldrin, dieldrin, chlordane, dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DDE) and dichlorodiphenyldichloroethane (DDD), as well as 2,3,7,8-TCDD and pentachlorophenol.

While benzo(a)pyrene would be expected in sediments, in fish it may be metabolized and excreted without significant accumulation in lipids.

Conversely, contaminants with medium-to-low Kow and medium-to-high solubility—such as toluene, trichloroethylene and phenol—would be expected to be found mainly in water phases, while toluene and trichloroethylene would volatilize appreciably from the water surface due to their relatively high vapor pressure and low K_H. In contrast, phenol with only a medium vapor pressure and high K_H, would not.

To illustrate how grouping tables can be applied to assess multiple chemicals in different classes for a cumulative risk assessment, we offer the following example for PCBs (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

TABLE 3-4

General Grouping Categories for Key Fate Parameters[a]

Parameter[b]	General Categories and Examples		
	Low	Medium	High
Partition coefficient Kow	<100	100-10,000	>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	10-1000	>1000
Henry's constant K_H *(mol/L*atm)*	<0.01 to 1	1-000	>1000
Vapor pressure VP *(mm Hg)*	<0.001	0.001-1	>1
Melting point MP *(^oC)*	<0	0-100	>100
Boiling point BP *(^oC)*	<50	50-300	>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). The melting point (MP) and boiling point (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	1280	87.2	69	-84.7
Phenol	29	3000	NA	83,000	182	0.35	40.9
Benzo(a)pyrene	1,300,000	2200	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
Mercury 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 multiple sources and are offered simply for illustration; to calculate environmental behavior for a specific case, setting-specific information may 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.

chlorination (e.g., more highly chlorinated compounds are less soluble). Additional data show that PCBs degrade slowly in soils (ATSDR, 2000c).

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 are expected to accumulate in the food chain; apex predators would likely have the highest concentrations.

The analysts can then explore grouping PCBs with other chemicals 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. 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. The implicit assumption in these examples is 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 process can

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*

*This table illustrates groups of chemical contaminants that may be expected to persist or be subject to degradation in various environmental compartments or phases, sometimes referred to as chemical sinks. These groups are based on sampling and analysis experience and are simply intended as a general indication of chemicals that may be combined in a cumulative risk assessment of exposures to a particular medium. (Note that chemicals are not limited to a single compartment.)

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 some cumulative risk assessments, it may be important to examine when these chemical movements would occur.

This concept is illustrated for an example release scenario (industrial spill) in Table 3-7. This concept applies to any environmental release, so other scenarios can also be considered, such as combustor emissions related to routine operations or temporary releases (e.g., due to excursions from a continuous-operation facility or discrete releases from a mobile facility). An approach for addressing that type of situation is illustrated in Figure 4-8.

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 3-8 (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.

Example of Possible Release Sources *(Text Box 3-8)*

To assess cumulative hazards of urban air toxics in the Chicago area, focusing on multiple releases to air was determined to be most useful. 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.

In this example, in order to identify the most significant sources leading to air contamination, the exposure analyst would consider 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). The exposure analyst would not conduct a quantitative fate and transport analysis 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

TABLE 3-7

Example Groupings Based on Exposure Considerations (Media and Timing)*

	Release Scenario		
	Industrial Spill on Soil near a River (VOCs, SVOCs and Metals)		
Exposure	Acute to Short-Term		Long-Term
Duration	<Day to weeks	Months	Years
Environmental Medium— Transport/Removal Process	Chemicals Projected to Be in Various Media over Time		
Soil upper horizon - volatilization and leaching from surface, biodegradation	CCl_4, DCA, DCE, TCE, VC; PCBs; As, Cd, Cr, Hg, Ni	PCBs; As, Cd, Cr, Hg, Ni	(possibly PCBs) As, Cd, Cr, Hg, Ni
Air - volatilization from soil	CCl_4, DCA, DCE, TCE, VC; PCBs	CCl_4; PCBs	(possibly PCBs)
Surface water (river) - overland flow and particle transport from surface soil	CCl_4, DCA, DCE, TCE, VC; PCBs; As, Cd, Cr, Hg, Ni	CCl_4, DCE, TCE; PCBs; As, Cd, Cr, Hg, Ni	(possibly PCBs)
Aquatic sediments - precipitation from water, adsorption on particles, deposition	CCl_4, DCE, TCE, VC; PCBs; As, Cd, Cr, Hg, Ni	CCl_4, TCE, VC; PCBs; As, Cd, Cr, Hg, Ni	PCBs; As, Cd, Cr, Hg, Ni
Soil lower horizons - leaching from surface soil, adsorption, biodegradation	CCl_4, DCA, DCE, TCE, VC; PCBs; As, Cd, Cr, Hg, Ni	CCl_4, TCE, VC; PCBs; As, Cd, Cr, Hg, Ni	PCBs; As, Cd, Cr, Hg, Ni
Groundwater - leaching from soil		CCl_4, DCA, DCE, TCE, VC	CCl_4, DCA, DCE, TCE, VC; PCBs; As, Cd, Cr, Hg, Ni

* Projected intervals reflect physical-chemical properties and fate data, including half-lives; other factors also affect partitioning and timing, including local conditions such as temperature (for volatilization); organic content (for soil and sediment sorption), which for this example is assumed to be relatively low; and depth to aquifer (for leaching to groundwater), which is assumed to be moderate to deep.
CCl_4 = carbon tetrachloride; DCA = 1,1-dichloroethane; DCE = 1,1-dichloroethylene; SVOCs = semivolatile organic compounds; TCE = trichloroethylene; VC = vinyl chloride.

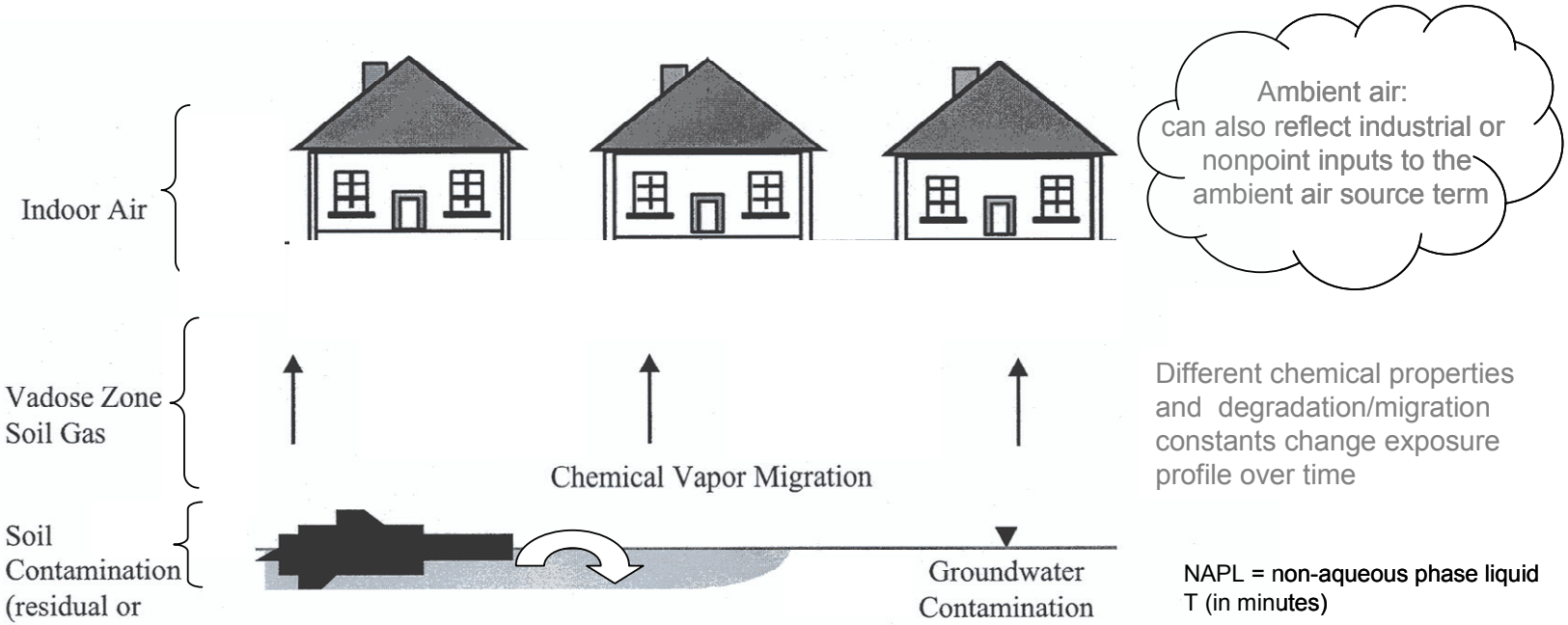
evaluation of contaminant fate and transport. Selected highlights are offered in the cumulative risk toolbox in Appendix A.

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 TCE, notably 1,2-dichloroethylene and vinyl chloride, as was described in Section 3.3.2.1 and as shown in Table 3-1. The concept of migration 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 (Vogel and McCarty, 1985) could actually pose greater health 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 risk 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:

- 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
- Weathering can change the composition of an original contaminant mixture

The composition of spilled oil has changed over time, as has that of the toxaphene mixture described in Text Box 3-9 (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



	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

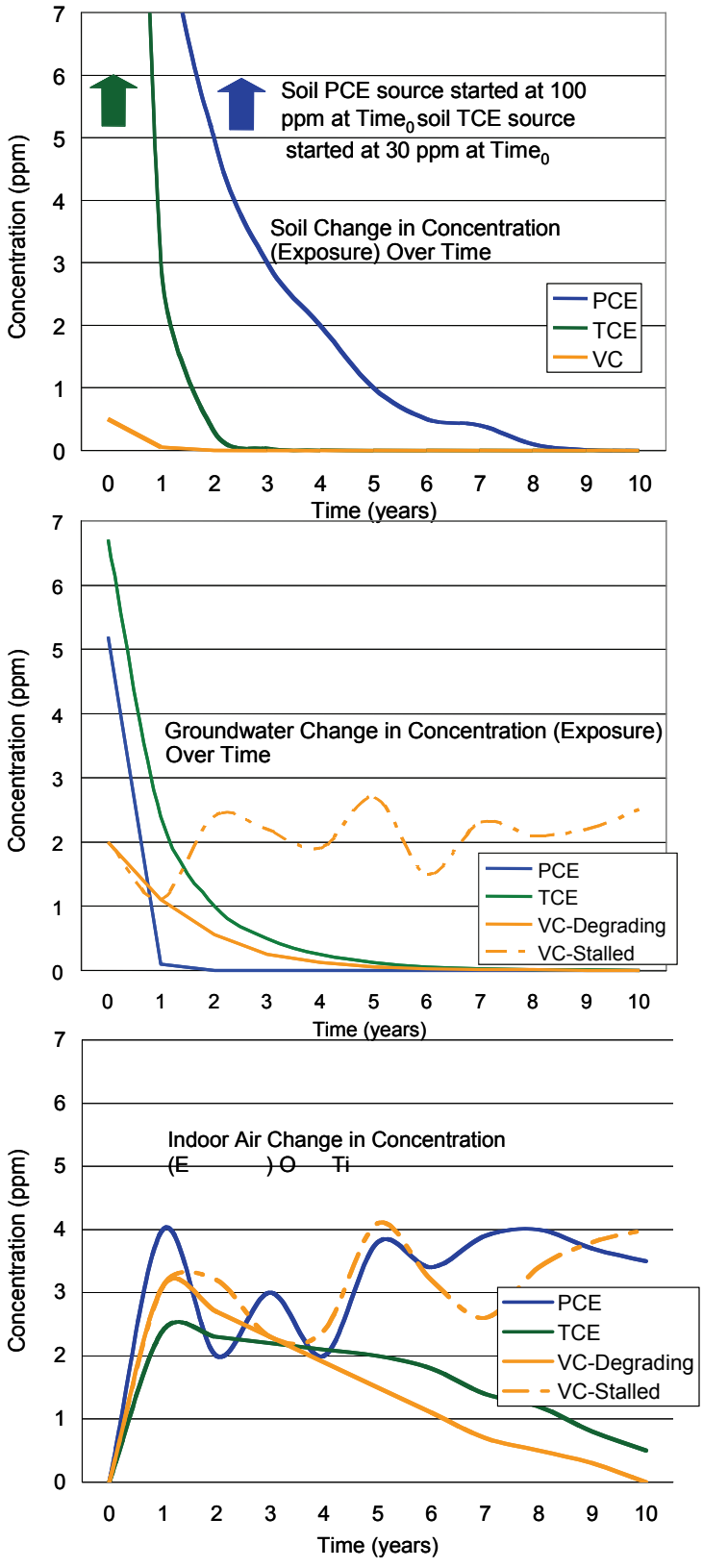


FIGURE 3-6
Illustration of Changing Media Concentrations Affecting Potential Exposures

partitioning equation and the use of either of two dilution attenuation factors (U.S. EPA, 1996a). This simple partitioning approach could be 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 be exposed to chemical pollutants, where and by what route(s) of exposure. The exposure points (the geographic locations where people could encounter the chemicals) and exposure routes are identified for each exposure pathway and then integrated for the cumulative risk assessment. The analyst also may consider interactions that might enhance exposures or associated effects and evaluate when these exposures may occur.

Weathering Example: Toxaphene *(Text Box 3-9)*

Until the 1970's, toxaphene was the most heavily used pesticide in the U.S. 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 can 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). Higher breathing rates for joggers running near an emission source is an example of an exposure factor that influences exposure. Higher breathing rates could result in an increased rate at which the jogger 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, the analyst integrates available information 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, at this point the analyst may consider relevant time frames of these exposures in order to examine the frequency, duration, intensity and possible overlaps of exposures to multiple chemicals as well as the sequence of those exposures. The exposure analyst

would consult with the dose-response analyst so that together they can determine the level of detail needed in the exposure assessment with respect to exposure overlaps. The dose-response analyst can provide information to determine 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 risk 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. An analyst could use the NHEXAS data 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, which contains chemical measurements, questionnaire responses, documents and other information related to U.S. EPA studies of human exposures to environmental contaminants (see Appendix A).

To evaluate what chemicals might coexist at places where individuals are--or could be--exposed, the analyst can group site-related contaminants by considering when they might coexist in space and time. This grouping could 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 3-10. 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, the analyst could then link these exposure groupings with toxicity information in order to assess joint impacts as described in Chapter 4. The analyst could evaluate these 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 3-10)

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

The EPA 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. Text Box 3-11 shows examples of chemical pairs for which the toxicological effect is influenced by exposure timing. Specific joint toxicity issues are discussed in Chapter 4. Several commercial exposure models have been developed to capture the time aspects of exposures, and Appendix A lists several of these.

Examples of Chemical Pairs Influenced by Exposure Timing *(Text Box 3-11)*

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

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
- 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 such a comprehensive exposure assessment would typically be beyond the scope of a contaminated site assessment project. The assessment may highlight the need for an evaluation of unknown sources of contaminants. The exposure analyst can use information offered in this report and many other resources 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. As was discussed in earlier sections, using models is the only way to estimate future contaminant concentrations. 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 a more detailed analysis, thus facilitating a more focused evaluation. Exposure analysts can use simple fugacity models to predict movement and phase change in the environment, for example, to identify which chemicals volatilize, stay soil bound or lodge in fat of fish or other food species. Environmental breakdown products also could be identified as indicated by the data or acknowledged as potentially present where those data do not exist. If resources are available, rare events that might result in different combinations of chemicals being released to the environment at higher levels may be considered. When describing the exposures that result from such events, the analyst may wish to describe the likelihood of such an event occurring.

The next step could be ranking 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, the exposure analyst could then apply exposure factors relevant to each receptor and then 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 0

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

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).

If available, the exposure analyst can use individual or community-specific exposure factors when estimating intakes, but generic default values are typically used in 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.

To illustrate the evaluation of multiple pathways and degradation products, we develop and present a hypothetical example depicting current and future land use at a fictitious contaminated site. Table 3-8 shows that at this site the receptors under current conditions are assumed to be an on-site maintenance worker and off-site resident. Exposure route-specific chemical intakes are illustrative only. Table 3-9 shows that at this site the receptors under future conditions are assumed to be an on-site resident and

TABLE 3-8

Example of Cumulative Exposures for Current Land Use*

Chemicals/ Transformation Products	Exposure Medium and Location	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}

TABLE 3-8 cont.

Chemicals/ Transformation Products	Exposure Medium and Location	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 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.

an off site visitor. In the current exposure scenario, exposures are analyzed following a chemical spill to surface soils. The spill subsequently leaches to subsurface soils and groundwater. 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. Exposure estimates will depend on the default and/or site-specific exposure factors used in the intake equations. To account for changes over time, cumulative intakes are calculated for exposures to original chemicals as well as to degradation products that can result from relatively rapid chemical reactions in the environment. 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 phase.

For a future land use scenario at the hypothetical contaminated site, an exposure analyst might identify two receptors: on-site residents and off-site recreational visitors. As presented in Table 3-9, exposures occur by several pathways that reflect a longer time frame (e.g., 20 years) than the current scenario. 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 phase.

3.3.3.3. Calendar Approach — While no EPA-wide standardized procedure exists for detailed consideration of exposure timing in dose/response assessment, the Office of Pesticide Policy provides an approach, identified as the calendar approach, in *General Principles for Performing Aggregate Exposure and Risk Assessments* (U.S. EPA, 2001a). Figure 3-7 provides an overview of the steps entailed in this 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 pesticides in the spring and summer) with routine exposures (e.g., contaminants in the food supply). Figure 3-8 illustrates a hypothetical pattern of results that could be predicted using such an 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.

TABLE 3-9

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}

TABLE 3-9 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 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.

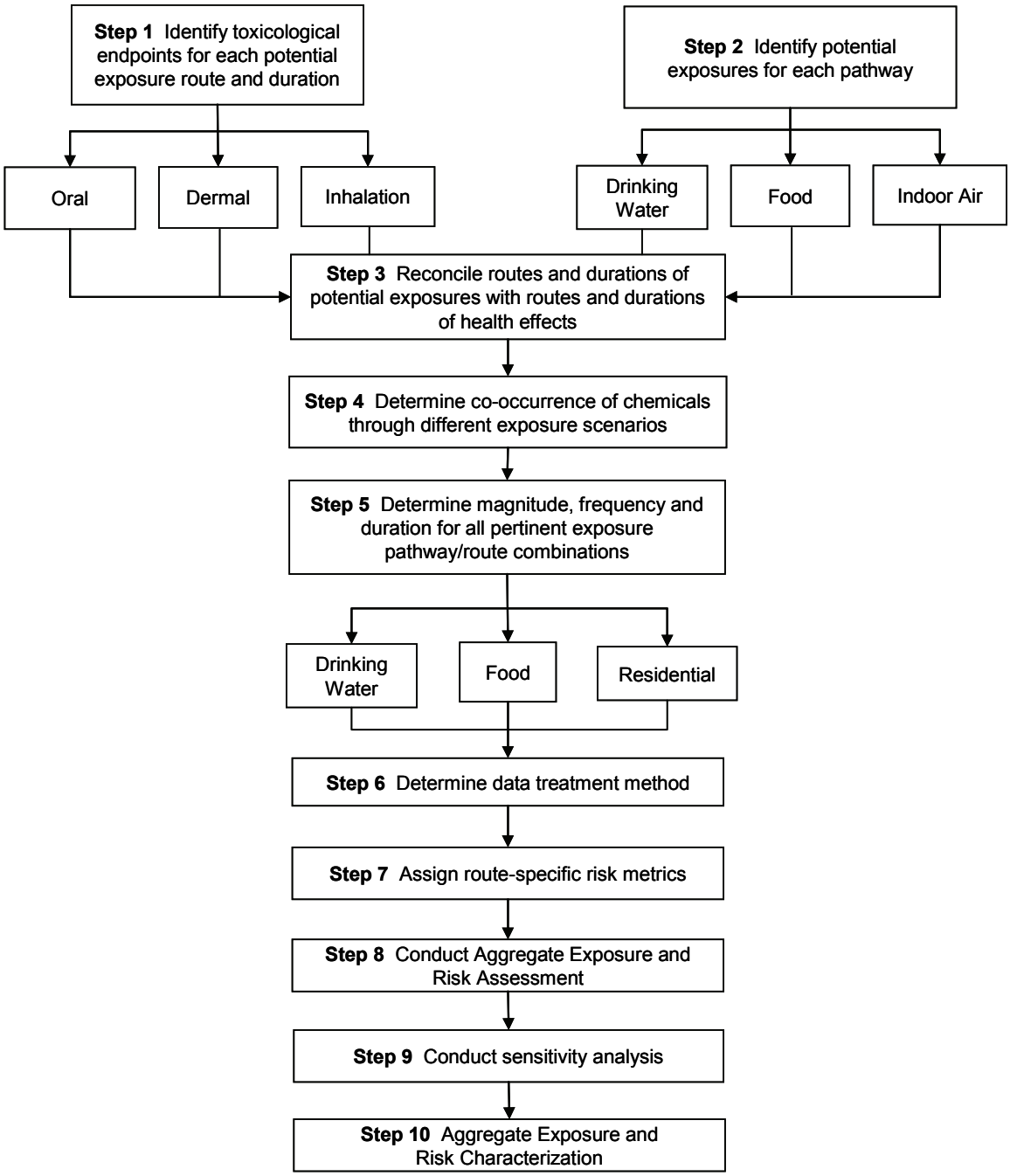


FIGURE 3-7

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

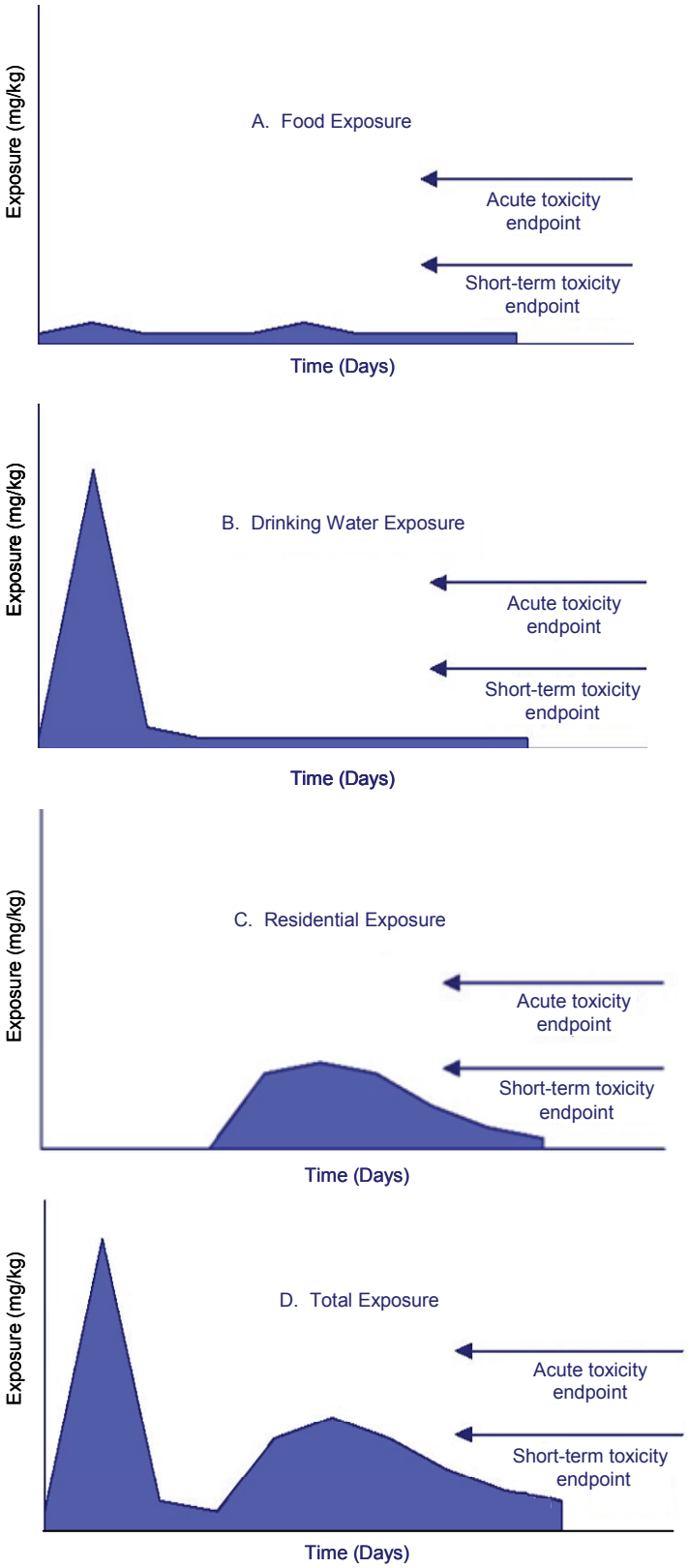


FIGURE 3-8

Pathway-Specific and Combined Exposure to a Single Hypothetical Chemical

The dose-response analyst and the exposure analyst work together on the first and third steps. The goal of these particular steps is to identify the health effect(s) associated with each chemical or group of chemicals identified. Health effect(s) identification includes an analysis of which exposure route(s) and exposure duration(s) produced the effect(s) (Step 1) and a step to ensure that the dose-response assessment and the exposure assessment are concordant (Step 3). A previous document (U.S. EPA, 1999e) describes five general durations of exposure to be considered:

- Acute – in a cumulative risk assessment this could include one-day exposures through oral (food and water pathways, which reflect distribution of daily food consumption and daily water residue values), inhalation (atmospheric concentrations) and dermal routes, which reflect daily water and soil residue values)
- Short-term – could include 1-30-day exposure scenarios
- Intermediate-term – could include 30-180-day exposure scenarios
- Chronic/long-term – could include exposures of greater than 6 months in duration
- Cancer – lifetime assessment

Following the identification of the toxicological 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). The exposure analyst accomplishes this by appropriately combining information about 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 involve 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 local-caught fish and commercial fish (i.e., two different sources of fish). An analysis could examine the correlation between consumption rates of local-caught and commercial 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 fish (e.g., in some areas of the U.S. there could be a decrease in local-caught fish consumption during winter). Furthermore, U.S. EPA (1999e) indicates that distributional data analysis (as opposed to a point estimate approach) is preferred

because this tool allows an aggregate exposure analyst to more fully evaluate exposure and resulting risk across the entire population rather than 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 exposure analyst would consider the hypothetical individual's temporal, spatial, demographic and behavioral exposure characteristics 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, the analyst logically would not assume independence (see Chapter 4). Instead, joint exposure can 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, e.g., multiple exposures may include inorganic mercury in soil and shellfish, DBPs in drinking water and during showering and volatile organic compounds in indoor air (originating from a site or from the use of household or office products). Such exposures could be combined in a cumulative risk assessment. Text Box 3-12 uses the chemical groupings based on

Examples of Chemical Groupings by Coexistence in Media/Time

(Text Box 3-12)

Time \ ***Media***	Same	Different
Same	Group 1 Co exposures to mixture of DBPs via consumption of unheated tapwater	Group 3 Co-exposures 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

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

Although, in general, less information is available to assess dermal exposures, this route can be important in cumulative risk assessments, depending on the specific exposures and contaminants involved. Guidance for assessing dermal exposures has continued to be refined as additional data and exposure assessment methods emerge (see U.S. EPA 2004a,h, and updates at http://www.epa.gov/oswer/riskassessment/ragse/).

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) describes a calendar approach that estimates daily exposures with occurrence 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[6] 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 multi-pathway 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 following applications to 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.

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

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 in different cumulative risk assessments. Figure 3-10 illustrates how an exposure assessment model was linked with a PBTK model for DBPs to estimate the 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 the analyst may need in order to perform 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

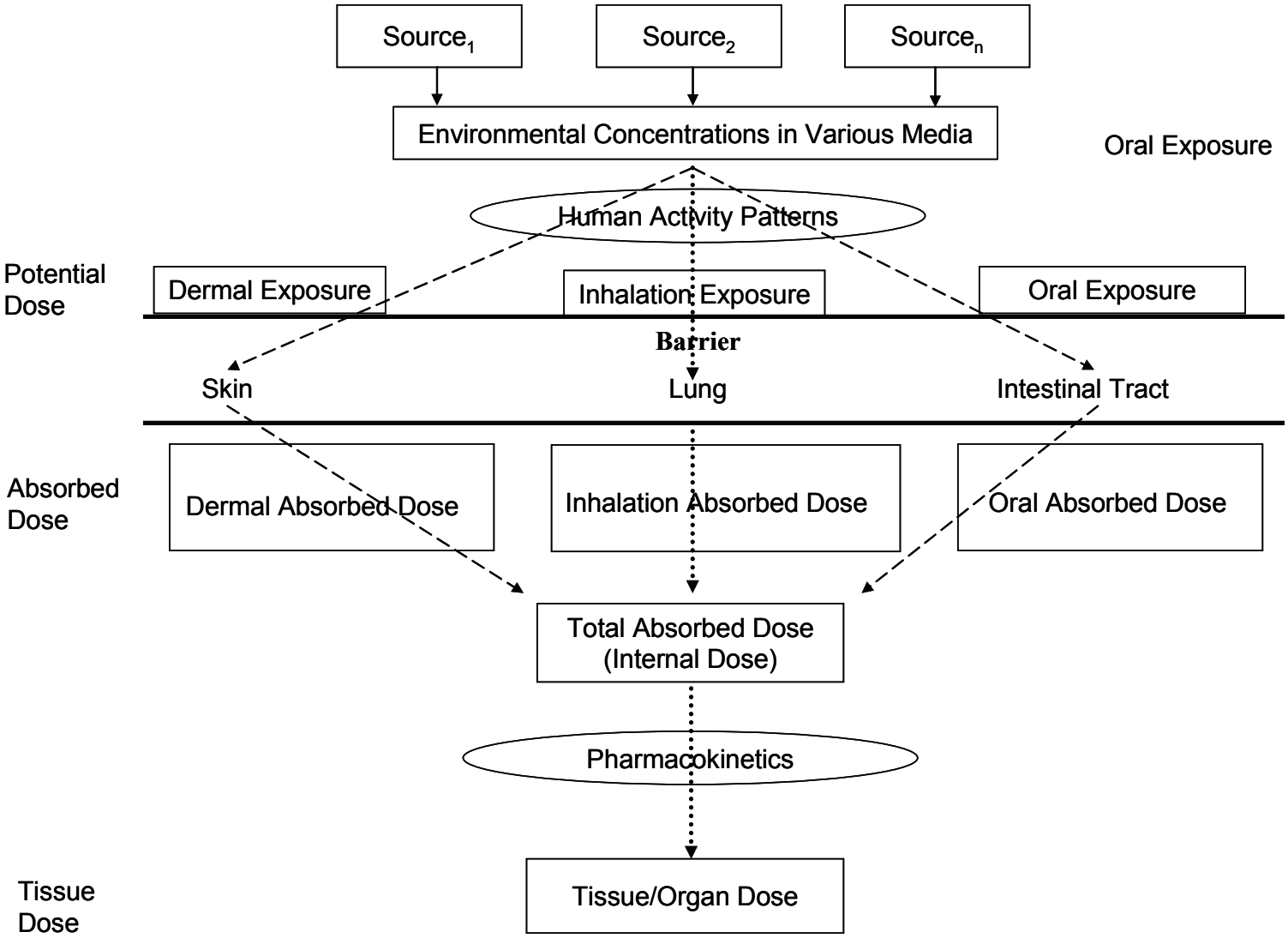


FIGURE 3-9

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

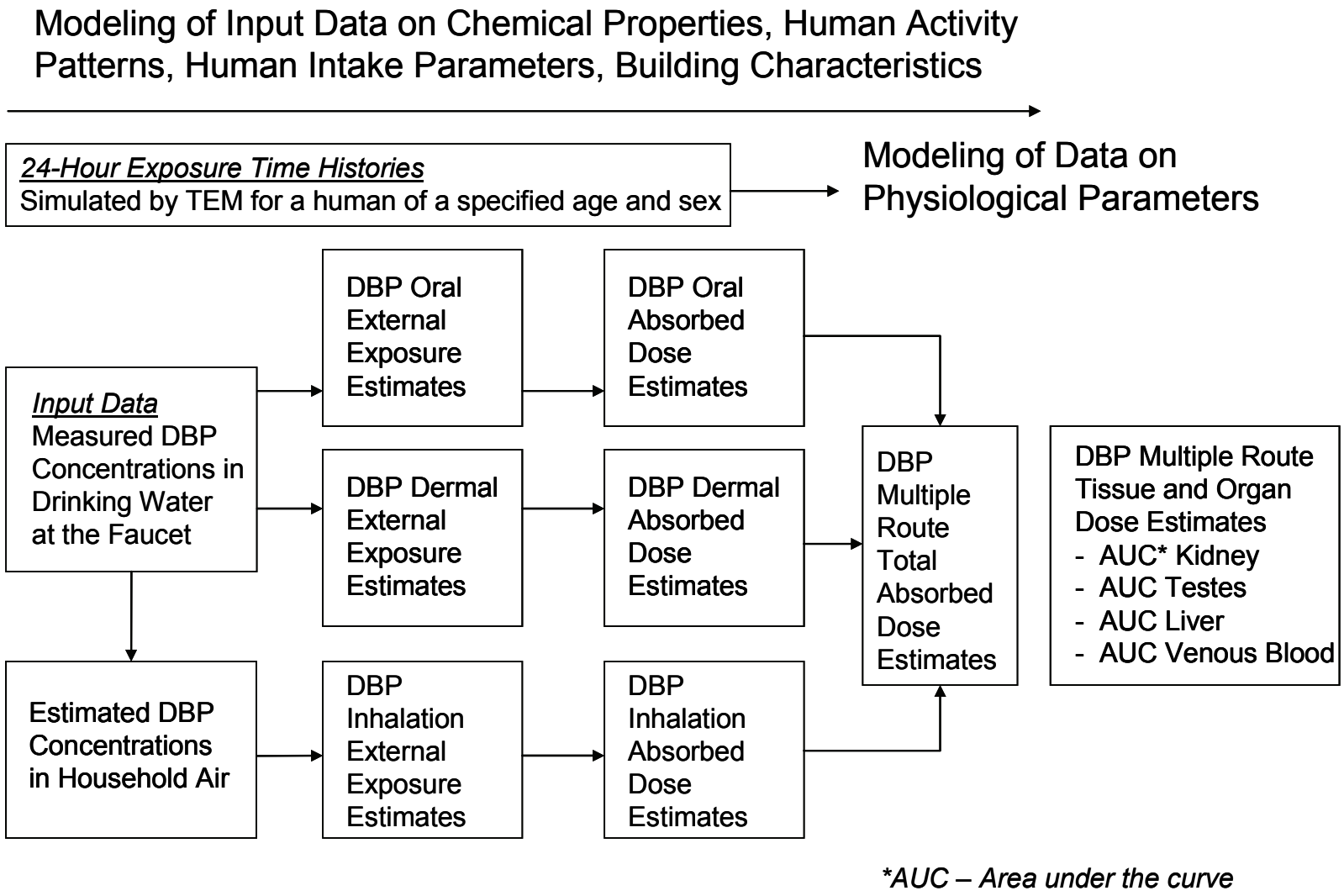


FIGURE 3-10

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

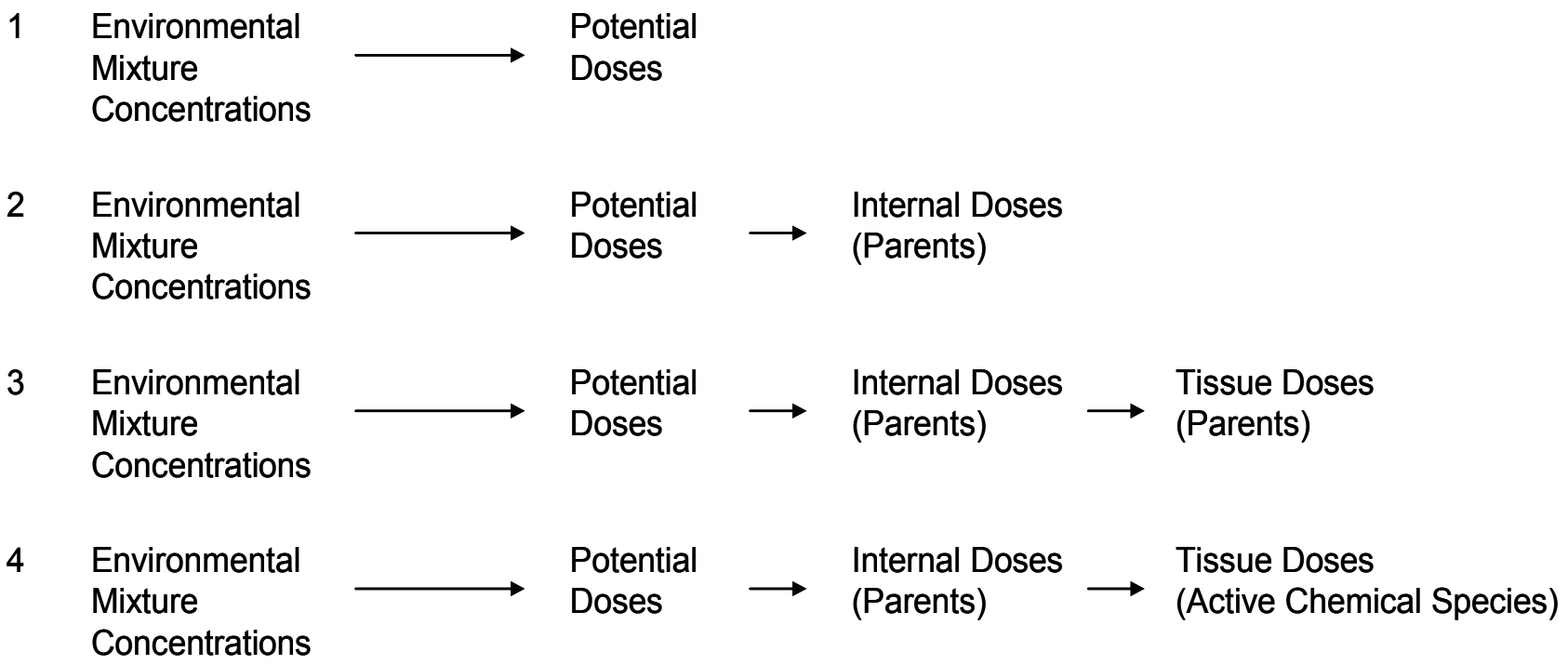


FIGURE 3-11

Levels of Dose Specificity that can be Estimated in a Cumulative Exposure Assessment

calendar approach). Depending on the variability of the exposures in the pathways, 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 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 Cr(III), Cr(VI) and tritium. The disposition of chemicals absorbed through different exposure routes may differ. The analyst may need to undertake an analysis as depicted in level 3 or 4 (Figure 3-11) 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 input concerning whether the compounds are toxic in their parent form or as metabolites. In turn, level 4 analysis predicts 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 exposure analyst would consult with the dose-response analyst to determine the level of detailed analysis necessary (level 1, 2, 3 or 4). 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) may be combined to allow a more complete 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 toxicodynamic effects including those based on chemical distribution and tissue effects. These effects can relate to subsequent

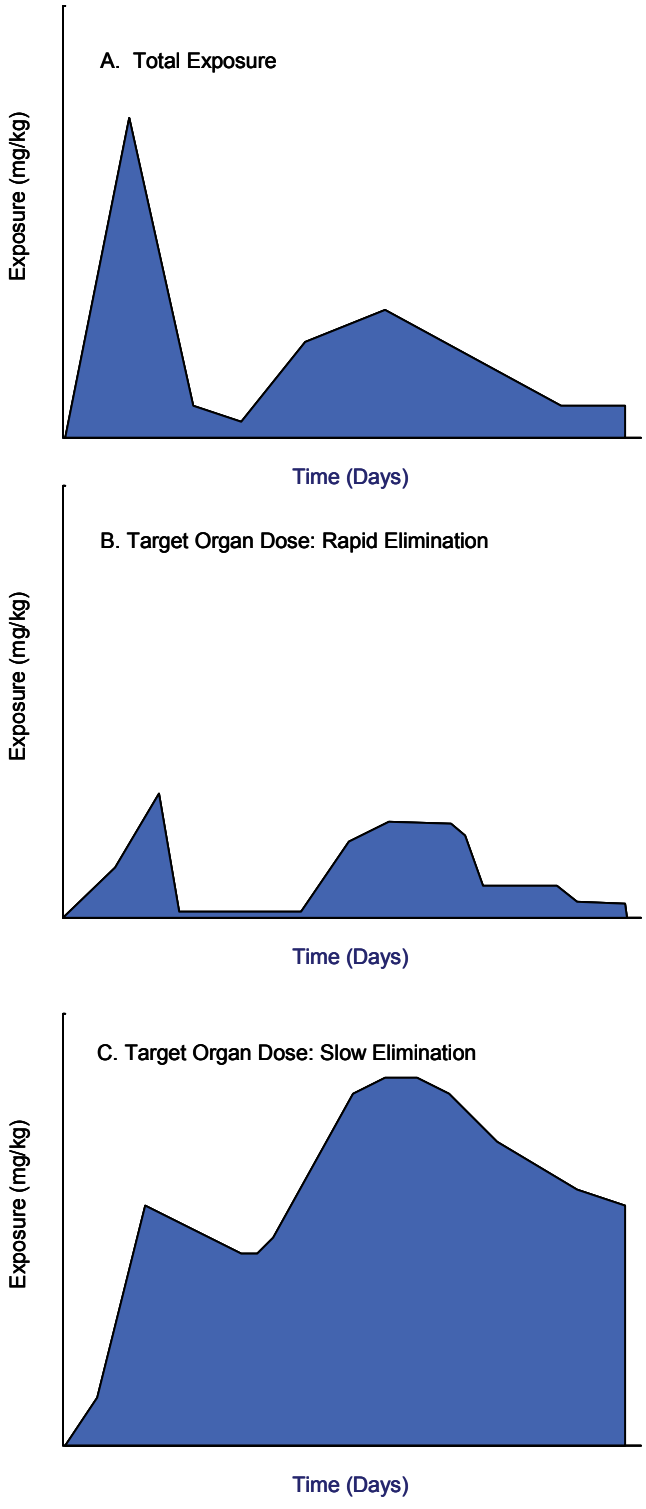


FIGURE 3-12
Multipathway Potential Doses and Target Organ Doses

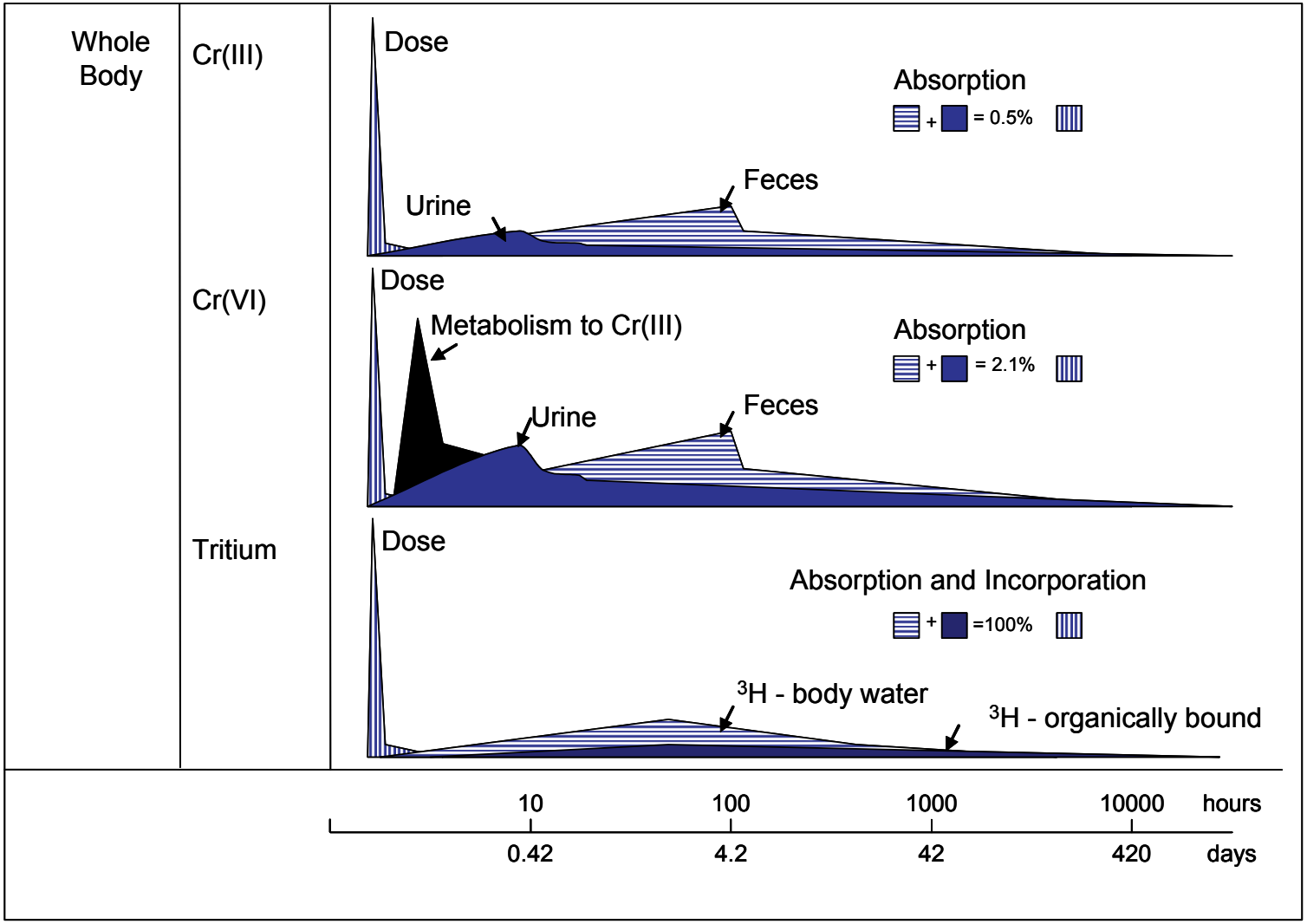


FIGURE 3-13
Human Residence Time for Selected Contaminants

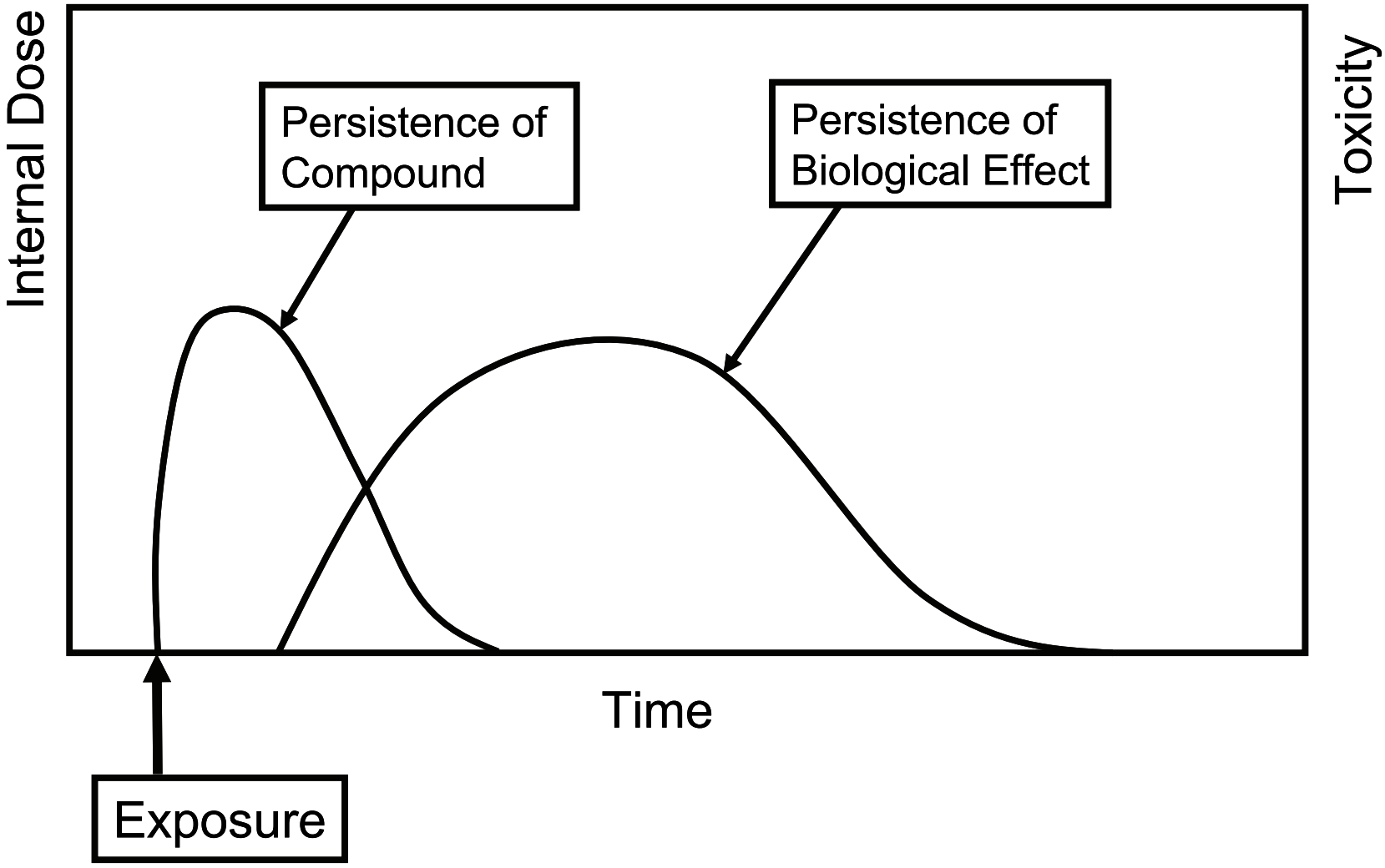


FIGURE 3-14

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

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 may be considered could be useful for cumulative risk assessments. The EPA 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.

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. 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. Tables within Appendix A include a number of tools that may help evaluate the groundwater pathway.

Several cleanup alternatives are typically evaluated for contaminated sites, ranging from no action (the baseline) 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 risk assessment are summarized in Text Box 3-13. 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 3-13)

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 usually are limited and air quality models can 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. With modeling results, analysts 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 tool available to help analysts assess impacts from hypothetical sources. They are valuable tools for assessing potential impacts associated with both existing emission sources and those projected during the cleanup period. Text Box 3-14 summarizes their benefit. Section 3.4.1 offers Illustrative information to guide the development of emission inventories for a cumulative risk

assessment at a contaminated site, and Section 3.4.2 gives information to guide dispersion modeling for these sites.

Benefits of Dispersion Models *(Text Box 3-14)*

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

Avoids detectability constraints, high monitoring costs

Identifies contributing sources to joint concentrations

Projects 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 3-15. At many sites, distinct areas of contamination can contain different combinations of chemicals at different concentrations.

Multiple Emissions During Cleanup
(Text Box 3-15)

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 slowly)

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

For cumulative risk assessments, clearly grouping the chemicals at each source area is important so that they can be appropriately scaled to the fugitive emissions estimated for that source. Proper grouping 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 EPA 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 risk assessment are also discussed, such as emissions of volatile and semi-

volatile compounds from disturbed soil. Text Box 3-16 highlights key resources. When using these and similar information sources, the analyst then can 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 3-16)

Information	Resource
Emissions from point and area sources	U.S. 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	U.S. EPA Clearing House for Inventories and Emission Factors (CHIEF) *(www.epa.gov/ttn/chief/)*

Of special interest for cumulative risk 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). An analyst can use tools developed by the EPA, such as those summarized in Text Box 3-17, to evaluate these and other mobile source emissions. As noted for Text Box 3-16, users can characterize their confidence in emissions estimates developed from sources, such as those cited in Text Box 3-17.

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).

Mobile Sources and Multiple Chemicals
(Text Box 3-17)

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-butadiene; 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.*

In many cases the particulate releases will dominate and other criteria pollutants will be negligible. For that situation the analyst could conduct a screening worst-case analysis 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 worst-case analysis showed that the non-particulate 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.

A cumulative risk assessment could include both types of releases. Text Box 3-18 summarizes the characteristics to consider in grouping PM and associated chemicals for these assessments. 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 3-18)*

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 PM emissions during cleanup can be estimated by considering 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 risk assessment an analyst may consider what materials are being combined together in order that representative concentrations of those materials can be appropriately grouped and scaled to the estimated emissions. For the second factor, production rates for each type of 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 3-19; many State environmental agencies have also developed standard approaches for examining such emissions.

Further, at many sites the contaminated source areas will be widely scattered. Thus, in estimating fugitive emissions for cumulative risk assessments, an analyst also

could consider when different areas will be remediated in order to properly group the emissions estimated for activities conducted in the same time period. Then the dispersion modeling can evaluate these sources jointly.

Example Particulate Factors *(Text Box 3-19)*

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.

Site-specific information to support such temporal exposure analyses are usually presented in the general contractor plans (i.e., these plans present a schedule for cleanup activities and list 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 EPA 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 http://www.epa.gov/scram001 as indicated in Appendix A.) Screening models involve relatively simple estimation techniques and generally use preset, worst-case meteorologic conditions to produce conservative estimates of the air quality impact of a specific source or source category. Analysts use these 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 the analyst would apply refined models for a more representative assessment. NRC (1994) discusses tiered analytic approaches extensively.

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.) Text Box 3-20 summarizes inputs to the model.

Air Dispersion Model Inputs *(Text Box 3-20)*

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

Meteorologic 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 risk assessment, the analyst can identify and group emission sources 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 analyst may wish to consider the presence of nearby buildings when performing a cumulative risk assessment, 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 no buildings are 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. Text Box 3-21 indicates additional considerations for modeling releases of multiple chemicals from a stack and for assessing impacts of multiple sources at multiple receptor locations (from U.S. EPA, 1985).

Example Model Input Considerations
(Text Box 3-21)

When the height of a stack for an existing or planned facility is lower than suggested by good engineering practice (GEP), building downwash can 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 meteorologic data inputs logically would represent site conditions. Some sites have meteorologic towers (such as larger federal research/industrial sites), but in many cases meteorologic 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. Text Box 3-22 highlights these inputs.

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, the analyst could 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 may be addressed in the uncertainty discussion (see Chapter 5). Similarly, when the analyst uses actual monitoring data, 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

Meteorologic and Receptor Data *(Text Box 3-22)*

Meteorologic 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 the 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.

within the breathing zone (on the order of 2 m), along with some discussion of data quality.

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 (and maximum concentrations for other time frames but not 24-hour estimates for complex terrain) (NRC, 1994). It also calculates the distance to the maximum concentration from the single source.

In order to apply this model for multiple release points, some analysts combine these multiple emission sources to be represented by a single theoretical point. In that case, the analyst likely would justify the basis 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 of assuming the emissions are released from a single point is that because of its conservative assumptions, it can generate quite unrealistic results, e.g., highly conservative values that expectedly would never be measured. Another disadvantage is the fact that this model for cumulative risk assessments cannot consider multiple sources, actual meteorologic 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 input to assess chronic effects. Thus, SCREEN3 results for the 1-hour period would need to be manually converted to other averaging times, and contributions from multiple sources would need to be combined to address cumulative issues.

To illustrate how this averaging time adjustment is made, U.S. EPA (1992b) provides scaling factors that are recognized as conservative and could overestimate impacts by 2-10 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 can 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 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 (also see discussion in NRC, 1994).

When more detailed analyses are needed, the analyst can use refined dispersion models. These include steady-state Gaussian plume models such as ISC3-PRIME or AERMOD. (They are available at www.epa.gov/scram001/tt26.htm#iscprime, www.epa.gov/ttn/scram/tt26.htm#aermod.) These models require relatively intensive efforts and computer resources. The main advantage of these models for cumulative risk 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 risk assessments by including dry and wet deposition algorithms, thus producing estimates an analyst can use 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. Text Box 3-23 provides a general comparison of the capabilities of screening and refined models for cumulative risk assessments.

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

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, an

analysts typically estimate dispersed concentrations 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 CMAQ modeling requires much more computer time than the steady-state Gaussian models so CMAQ models would probably not be appropriate for most site assessments.[7] 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. To date, the Agency only has released results from the CMAQ model for mercury (U.S. EPA, 2005g).

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 also could 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.

[7] In addressing fate and transport over time, time-dependent models can yield better estimates of exposure point concentrations than steady-state models. However, computational and resource requirements can be much more extensive as these models are not amenable to a simple spreadsheet approach, relying on programming language or solved using special macros. In any case, even these models cannot generally represent truly accurate calculations, with inherent uncertainties and unknowns as for all models. A model is considered very good when it can predict concentrations within a factor of 2 of measured results. For time-dependent models, while the value of the predicted maximum concentration across all locations can be reasonably accurate, its predicted location is not generally as accurate. The need for accuracy could be weighed against the availability of resources.

3.5. RETROSPECTIVE STUDIES

In many cases, a cumulative risk assessment will involve predicting health outcomes from combined estimates of exposure based on a combination of point concentrations (e.g., site-specific measures of chemical concentrations in specific environmental media), exposure factors and toxicity data. However, in other cases, observed health effects could initiate the cumulative risk assessment. Dose reconstruction studies, or retrospective exposure assessments, can be used to support risk analyses when health outcomes are observed. The aim of these studies is to reconstruct the doses that occurred to assess potential contributions of past exposures to the indicated health effects.

Dose-reconstruction studies are typically constrained by data limitations for location-specific concentrations for the relevant chemical forms in the given media over the period of interest as well as specific exposure patterns. Further complications include the inability to control for lifestyle factors such as smoking because those data are often not available in the historic records. Nevertheless, a number of dose reconstruction studies have been conducted to support occupational and environmental health risk analyses. These include dose reconstruction studies for people at U.S. Department of Energy (U.S. DOE) facilities (e.g., see Stange et al., 2001; also http://www.cdc.gov/niosh/ocas/ocasdose.html) as well as for people exposed to radiation from nuclear weapons tests and explosions that began more than 60 years ago (NRC, 2003a). To illustrate how difficult it can be to reconstruct doses in the face of considerable data limitations, in some cases the concentrations in the locations of interest (where people lived) had to be modeled from measurements reported for monitoring stations hundreds of miles away in complex terrain.

Similarly, historic occupational data also have limitations, with specific exposure patterns and concentrations documented poorly if at all, such that average and peak concentrations and durations are difficult to estimate in order to assess cumulative daily and repeat exposures. As a reflection of the increasing emphasis on this tool, the National Academy of Sciences (NAS) recently reviewed previous dose-reconstruction studies to assess whether the methods and data used were accurate, the reconstructed doses were accurately reported and the exposure assumptions were credible. The NAS concluded that although the methods were generally valid, resultant estimates were highly uncertain because specific data were either sparse and highly variable or simply lacking. A key conclusion was that the review and oversight of dose-reconstruction studies should be commensurate with the anticipated scope of the compensation program (NRC, 2003b). This same principle applies to the level of cumulative risk

analysis, i.e., that resources applied are commensurate with the needs of the decision to be informed.

3.6. SUMMARY COMPARISON AND SCREENING SUGGESTIONS

Text Box 3-24 summarizes a general comparison of the exposure assessment process conducted for basic health risk assessments and for cumulative exposure assessments.

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

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 risk assessments at these sites are offered below, with an emphasis on screening for grouped evaluation.

- 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 (1) 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, (2) in addition to those with high inherent hazard (toxicity) in combination with (3) the amount present; (4) potential interactions with other chemicals; and (5) tendency to persist, bioaccumulate and/or be transported between environmental media.
- To screen potential vulnerable or susceptible subgroups into the enhanced cumulative risk 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. TOXICITY ASSESSMENT OF MULTIPLE CHEMICALS, EXPOSURES AND EFFECTS

This chapter provides detailed information on the toxicity assessment of multiple chemicals, exposures and effects, a subset of cumulative risk issues that are described in Chapters 1 and 2. The goals of Chapter 4 are to

- define cumulative toxicity assessment as conducted in this chapter (Section 4.1);
- summarize existing EPA guidance for conducting toxicity assessments, including chemical mixtures risk assessments (Section 4.2); and
- expand those ideas to 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).

Section 4.4 presents a flow chart for the purpose of facilitating and organizing the analyst's effort to evaluate toxicity groups for cumulative toxicity assessment. The approach presented in this chapter provides a method for grouping 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 a set of cumulative risk assessment methods for addressing multiple toxic effects, multiple exposure routes and toxicological interactions for chemical mixtures. These methods may be used in cumulative risk assessment in several different ways depending on data availability and on the goals of the assessment. They may be applied as screening tools (e.g., to decide whether or not toxicological interactions are of importance for a certain group of chemicals) or as tools for estimating quantitative risk numbers (e.g., estimating the risk of an adverse level of cholinesterase inhibition by applying a Relative Potency Factor [RPF] approach to a group of pesticides). In some cases all of the methods shown in this chapter might be applied, and in other cases, only a select few methods would be useful depending on the exposure scenario.

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 EPA with data sources and methodology for conducting such assessments.

4.1. DEFINING CUMULATIVE TOXICITY ASSESSMENT

Toxicity assessments developed in this chapter in support of cumulative risk assessments evaluate a population's potential to develop adverse health effects from exposures to multiple chemicals through multiple routes of exposure over time. In addition, such assessments may consider the potential for multiple health effects and for joint toxic action from multiple route exposures to chemical mixtures. Timing and intensity of exposures to different chemicals may be evaluated, including the examination of internal co-occurrence of multiple chemicals and toxicological interactions in the target tissue(s).

The development of methods in this chapter are narrowly constrained to multiple chemicals, exposures and effects; thus they will aid the analyst in conducting a cumulative toxicity assessment, but they may be augmented with additional information and analyses in order to produce a more comprehensive, community focus, where the population may be exposed to stressors other than chemicals, potentially from multiple sources. In addition, information developed during data collection and organization regarding the population profile may be further incorporated, including considerations related to vulnerability (i.e., susceptibility/sensitivity, differential exposure, differential preparedness and differential ability to recover).

4.2. TOXICITY ASSESSMENT GUIDANCE AND METHODS

The general methods the EPA uses for toxicity assessment are detailed in a number of risk assessment guidelines and guidance documents, as illustrated in Text Box 4-1. The EPA's 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 EPA's Web site (www.epa.gov). For example, to supplement its primary guidance for site assessments (U.S. EPA, 1989a),

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, 1986b, 1987)
Risk Assessment Guidance for Superfund (U.S. EPA, 1989a)
Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991a)
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, 2005d)
Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (U.S. EPA, 2005e)

Superfund provides a set of tables to be used as templates for conducting HI 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 2000 *Supplementary Mixtures Guidance* (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 exposures (U.S. EPA, 2002c) and for mechanisms of carcinogenicity (U.S. EPA, 2005d). The assessment of vulnerable subpopulations is also addressed by Superfund in their site assessment guidance (1989a). Children are specifically addressed in a supplemental guidance to the 2005 carcinogen risk assessment guidelines (U.S. EPA, 2005e). In summary, there are many EPA 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. Practices for Evaluation of Toxicity for Various Durations. In toxicity assessment, Reference Values (RfVs)[1] are often used as target levels that are protective of human health. The focus of most site assessments is on evaluating health effects from chronic exposures. However, shorter-duration exposures can also play a key role in risk assessments, such as the evaluation of remediation activities at contaminated sites. For example, health effects are assessed for workers and the public from short-term exposures to releases associated with cleanup measures, such as excavation or treatment processes for contaminated materials.

The *Risk Assessment Guidance for Superfund* (U.S. EPA, 1989a) outlines approaches for evaluating potential health effects associated with different time frames, using RfVs developed for exposure duration. More recently, the NRC discussed the issue of varying exposure durations and selection of corresponding RfVs in its Review of the Army's Technical Guides on Assessing and Managing Chemical Hazards to

[1]Reference Value (RfV): EPA's 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. Durations include acute, short-term, subchronic and chronic. EPA develops numerical toxicity values for the oral RfD and inhalation RfC. (See the Glossary in Chapter 7 for complete definitions.)

Deployed Personnel (NRC, 2004). RfVs have been and continue to be developed for chronic exposures. However, RfVs for shorter durations are also available for a more limited number of combinations of chemicals and exposure durations, some of which might deviate from the assumed constancy of the concentration * time product (see the glossary in Chapter 7 for complete definitions). Table 4-1 highlights selected, additional RfVs.

As noted by NRC (1994), chronic RfCs and RfDs can also be examined to determine if an Uncertainty Factor (UF)[2] of 10 was applied in the original derivation for subchronic to chronic extrapolation. In this case, it may be appropriate to multiply the chronic RfC or RfD by a factor of 10 for evaluating less than chronic exposure durations. Further, some chronic RfVs may be appropriately applied to shorter exposure durations (in the absence of an RfV derived for the duration of interest), particularly for chemicals whose toxicity is more a function of concentration than cumulative exposure. It is important to discuss the uncertainty or confidence in the values used within a risk assessment, giving consideration to the correspondence between the context and exposure duration for which the RfVs were developed and then applied in the risk assessment and their source and the nature of their RfV development process.

4.2.2. Practices for Evaluating Chemical Mixtures. The EPA evaluates risks from exposure to chemical mixtures using peer-reviewed Guidelines and Guidance documents (U.S. EPA, 1986b, 1989a, 2000a) that identify both component-based and whole mixtures methods. The flow chart from U.S. EPA (2000a), shown in Figure 4-1, illustrates that the selection of a method (e.g., HI, RPF) depends on the availability and interpretation of information on toxicological joint action and chemical composition of the mixture.

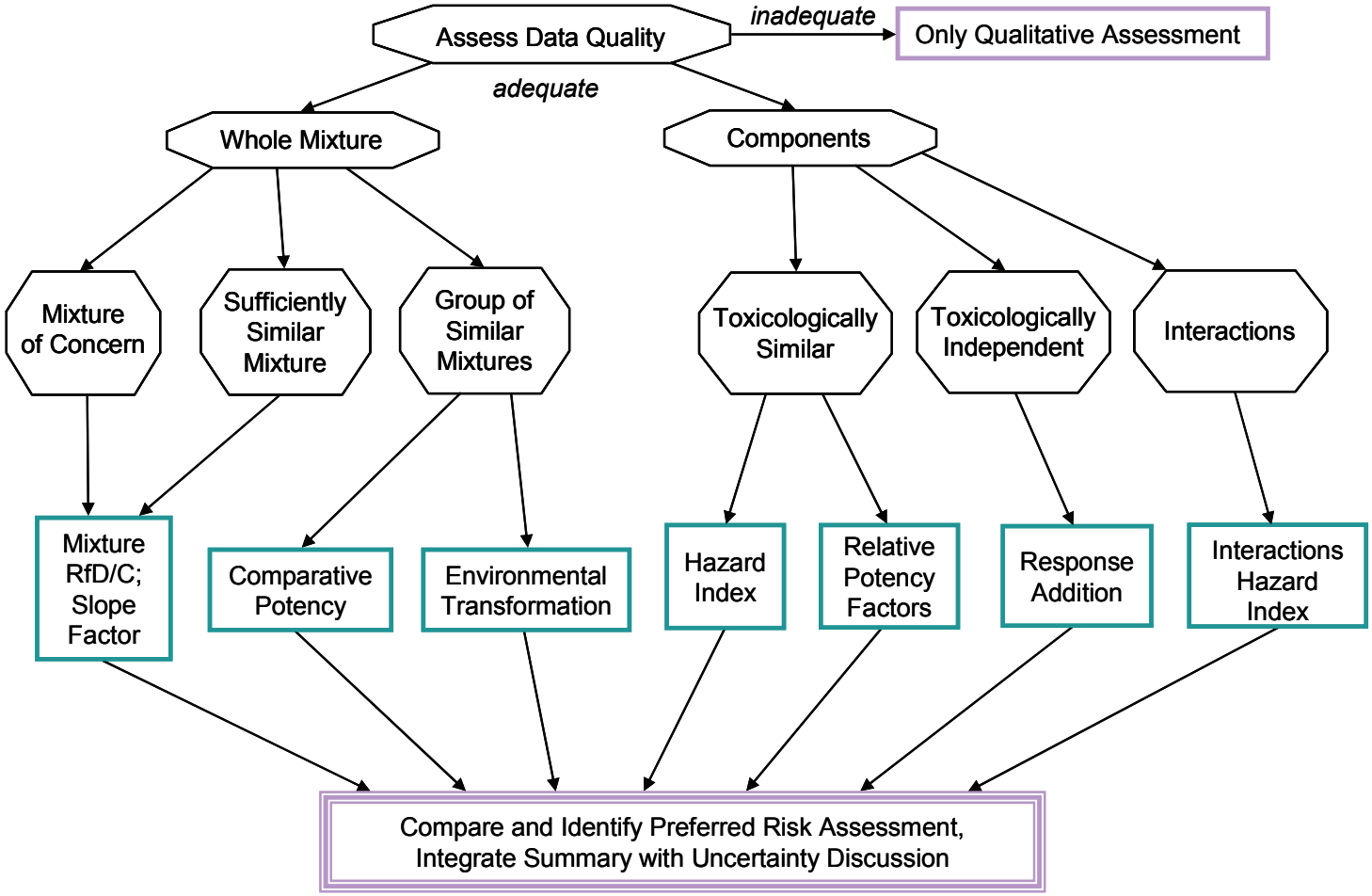
Whole mixture methods (e.g., mixture RfDs, RfCs and cancer slope factors) account for unidentified chemicals in a complex mixture and inherently incorporate joint

[2] Uncertainty/Variability Factor (UFs): One of several, generally 10-fold, default factors used in operationally deriving the RfD and RfC from experimental data. The factors are intended to account for (1) variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability); (2) uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); (3) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); (4) uncertainty in extrapolating from a lowest-observed-adverse-effect level (LOAEL) rather than from a no-observed-adverse-effect level (NOAEL); and (5) uncertainty associated with extrapolation when the database is incomplete.

TABLE 4-1

Selected Reference Values for Different Exposure Durations

Exposure Duration	Toxicity Value or Guideline	Source	Notes
Acute (<24 hours)	1-day drinking water health advisory	EPA Office of Water http://www.epa.gov/waterscience/criteria/drinking/	Based on oral toxicity values derived by the EPA Office of Water
	Acute exposure guideline level (AEGL)	National Advisory Committee, National Research Council	Derived for inhalation exposures for exposure times ranging from 10 minutes to 8 hours
Short Term (1-30 days)	Acute minimal risk level (MRL) (1-14 days)	ATSDR (http://www.atsdr.cdc.gov/mrls.html)	Based on oral or inhalation toxicity values derived by ATSDR
	10-day drinking water health advisory	EPA Office of Water http://www.epa.gov/waterscience/criteria/drinking/	Based on oral toxicity values derived by the EPA Office of Water
Longer Term (>30 days to 7 years)	Intermediate MRL (15-364 days)	ATSDR (http://www.atsdr.cdc.gov/mrls.html)	Based on oral or inhalation toxicity values derived by ATSDR
Chronic (>7 years)	Chronic reference dose and concentration	Integrated Risk Information System (IRIS) http://www.epa.gov/iris/	For oral and/or inhalation exposure
	Chronic MRL (>1 year)	ATSDR (http://www.atsdr.cdc.gov/mrls.html)	Based on oral or inhalation toxicity values derived by ATSDR



The different types of mixtures assessments based on the availability and quality of the data. All possible assessment paths should be performed.

FIGURE 4-1

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

toxic action among chemicals (Figure 4-1).[3] Dose response assessments based on tests of whole mixtures or on epidemiologic data determine combined effects empirically. Examples of these (U.S. EPA, 2007) include (1) RfDs 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.

The usefulness of toxicological 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 that is being considered as a surrogate has roughly the same major chemical components in approximately the same proportions as the environmental complex mixture that is being evaluated. Any additional information on toxicological 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 overall similarity. The EPA's 2000 *Supplementary Mixtures Guidance* discusses several issues with determining toxicological similarity of two complex mixtures (U.S. EPA, 2000a). For example, the RfD, RfC 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 challenge for an analyst to ensure that the mixture composition (relative proportions of the component chemicals) remains fairly constant.

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 with varied concentrations and proportions. Component-based methods include those based on assumptions of response addition (toxicological independence) and dose addition (toxicological 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 HI method may be applied, using information on binary (pairwise) interactions among chemicals in a mixture to modify its HI (see Section 4.6.2 for details on this method). The main toxicological considerations for the component-based risk assessment methods used by U.S. EPA are then toxicological independence, toxicological similarity and pairwise interaction.

Dose addition and response addition are fundamentally different methods, relying on different toxicity assumptions. The two additivity assumptions are briefly described

[3]It may be noted here that this chapter does not employ the comparative potency or environmental transformation methods shown in Figure 4-1; thus, they will not be described further.

in the following text. Extensive discussion of these mixture methods is given in the EPA's 2000 *Supplementary Mixtures Guidance* (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]). If dose addition is applied using an index chemical to estimate risk, 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.

4.2.2.1. Dose Addition — Superfund site assessments have applied dose addition in the form of a HI to evaluate sites for indications of health risk (U.S. EPA, 1989a). The HI is calculated as the sum of 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:

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

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 RfC for the allowable level. The HI is usually calculated for groups of chemicals whose effects are observed within a common target organ. The HI is interpreted similarly to the HQ: 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, also based on dose addition, uses RPFs for the dose scaling. Because the total dose of the chemicals in

the mixture is of importance, the chemical components of a mixture are scaled for relative toxicity to an index chemical and then 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):

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 is 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 noncancer endpoints only) for use in target organ specific HI calculations (Mumtaz et al., 1997; U.S. EPA, 2000a).

Appropriate interpretation of the HI requires 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]

4.2.2.2. 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. Total cancer risk is then estimated for a mixture by summing the individual cancer risks for the carcinogens in the mixture (U.S. EPA, 1989a). This calculation is derived using the statistical law of independent events, where, for a two chemical mixture, the mixture risk (R_m) is equal to one minus the probability of not responding to either chemical 1 (r_1) or chemical 2 (r_2):

[4]The critical effect is defined as the first adverse effect, or its known precursor, that occurs to the most sensitive species as the dose rate of an agent increases.

$$R_m = 1 - (1 - r_1) * (1 - r_2) \quad (4\text{-}2)$$

Simplification of this equation shows that 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:

$$R_m = r_1 + r_2 - (r_1 \times r_2) \quad (4\text{-}3)$$

When risks are very low, the subtracted term is so small that its impact on R_m is negligible (e.g., for r_1 = 0.01 and r_2 = 0.02, R_m:= 0.01 + 0.02 – 0.0002 = 0.0298 or ~0.03); thus, low risks can simply be summed. 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 are typically accompanied by a description of the evidence supporting the additivity assumptions, i.e., commonality of toxicity for dose addition and toxicological independence for response addition.

4.2.3. Old, New and Enhanced Approaches for Cumulative Toxicity Assessment. Cumulative risk assessments add layers of complexity to evaluation of chemical mixtures. Figures 4-2a and 4-2b take the concepts developed in Figure 4-1 and expand them by presenting both established methods along with new or enhanced methods that may be used to evaluate various aspects of cumulative risk. For example, Figure 4-2a shows the same development of toxicity values (i.e., RfDs, RfCs and slope factors) as presented before for whole mixtures and sufficiently similar mixtures, but Figure 4-2a now includes additional epidemiologic evaluations that may be conducted when illnesses in the population initiates a cumulative risk assessment (discussed in Section 2.5). Figure 4-2b also maintains previously used component-based chemical mixtures methods (i.e., RPFs, HI, Response Addition and the Interaction-Based HI), but several other approaches are also reflected in this figure, and these will be presented and discussed later in this chapter. Further, Figure 4-2b handles not only toxicologically similar and dissimilar mixtures, but the figure also addresses mixes of these, as well as addressing the case of multiple toxicological effects. Finally, additional methods are

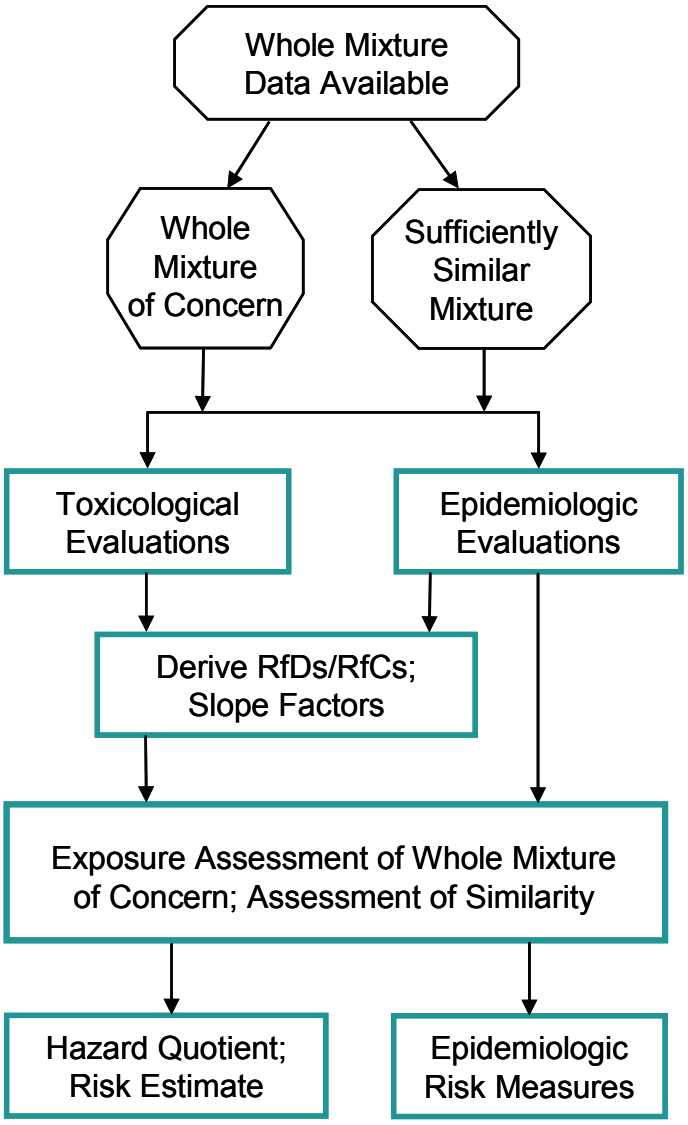


FIGURE 4-2a
Flow Chart Showing Approaches for Evaluating Whole Mixtures

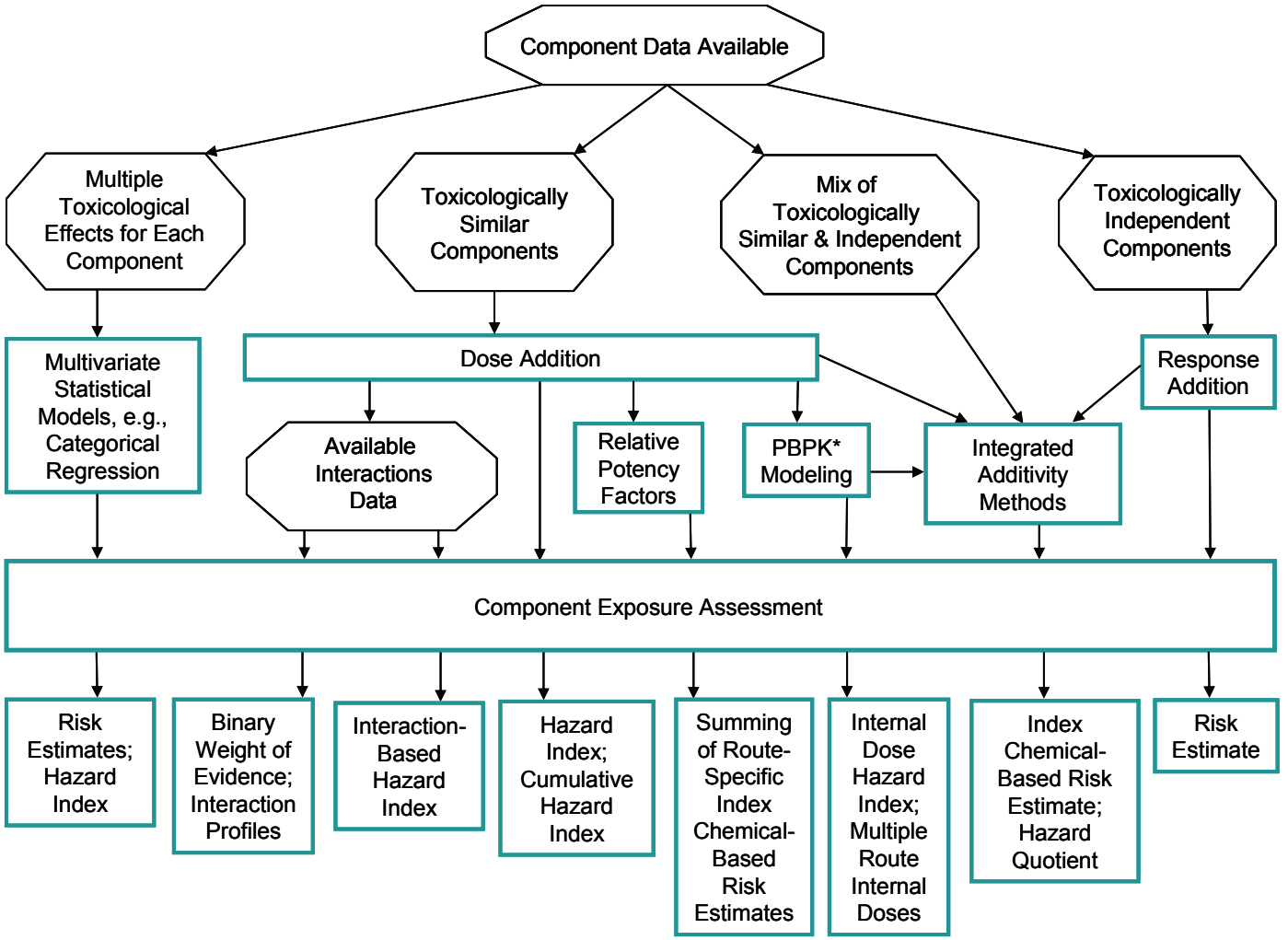


FIGURE 4-2b

Flow Chart Showing the Component Based Approaches for Evaluating Multiple Chemicals, Exposure Routes, Effects and Toxicological Interactions

discussed that include the use of PBPK models to estimate internal doses of chemicals and examine the potential for toxicological interactions.

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 EPA 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 4-3). 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 allow 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; each is useful and differentially resource-intensive.

Metabolites can have a different, or even opposite action, from the parent compound, further complicating an assessment. For example, Gierthy et al. (1997) report that the PCB 3,4',5-trichlorobiphenyl shows antiestrogenic activity in an *in vitro* assay, whereas its hydroxylated metabolite shows strong estrogenic activity. As more is learned about mixtures of the same general class (e.g., dioxins/furans, PCBs,

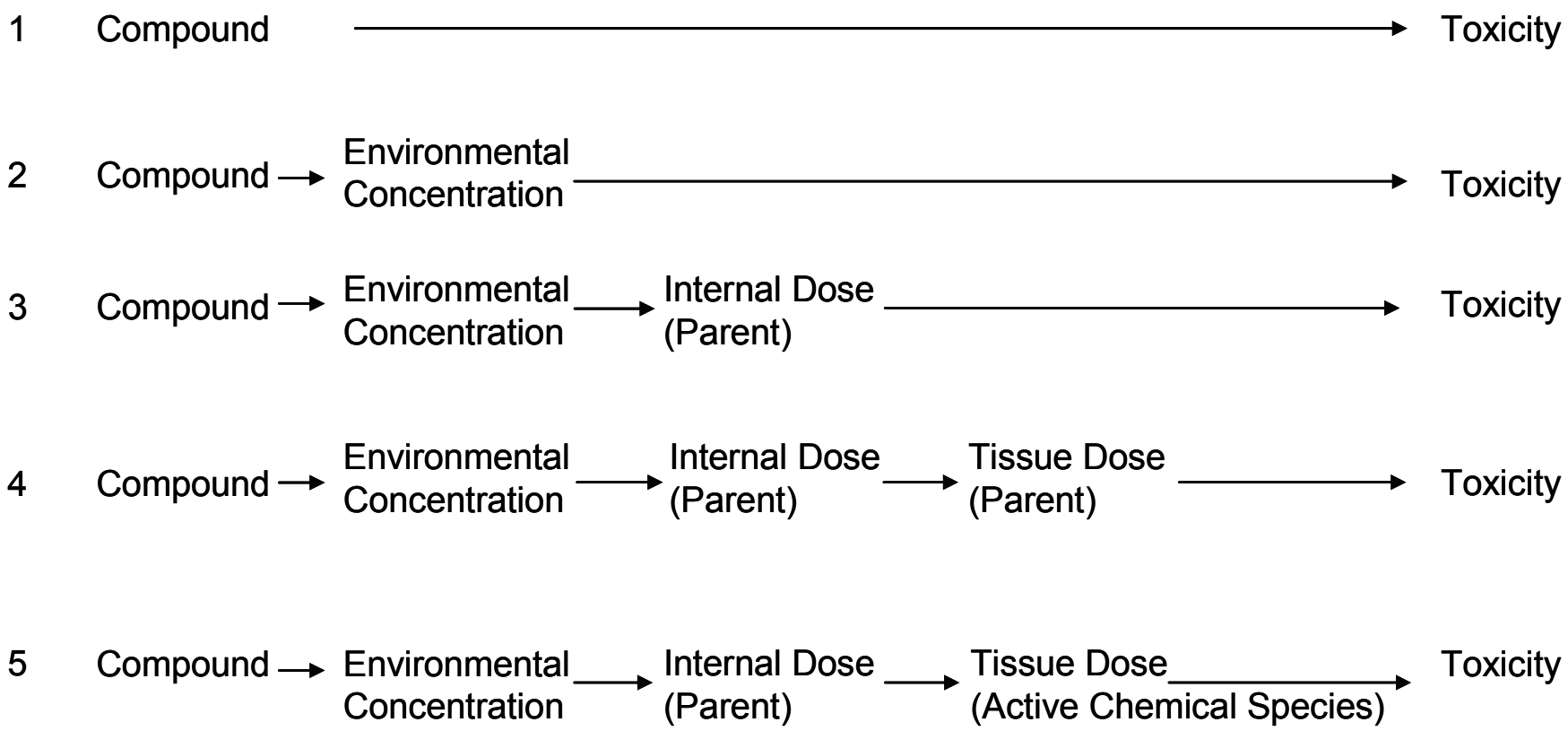


FIGURE 4-3
Level of Specificity for Dose-Response Relationships

polybrominated diphenyl ethers, and toxaphene) and their specific biological effects, further refinements may be incorporated into an assessment.

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 summarizes information demonstrating the biological longevity of contaminants to determine potential overlap of tissue concentrations (Figure 4-4, also discussed from an 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) are 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 4-5, also 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 4-6). 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

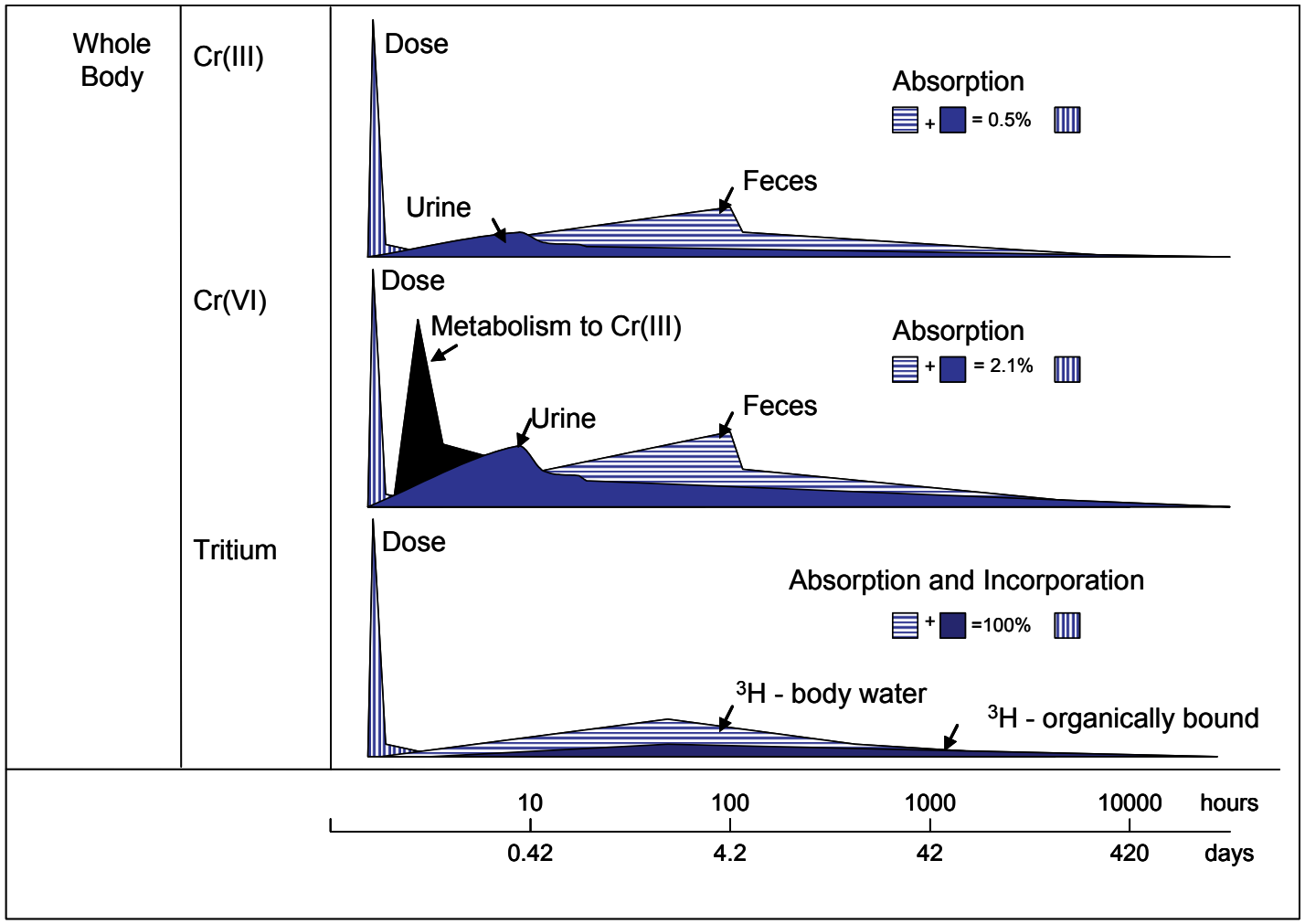


FIGURE 4-4
Human Residence Time for Selected Contaminants

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 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 is determined, and its impact on the toxicity of other compounds is investigated on a compound by compound basis.

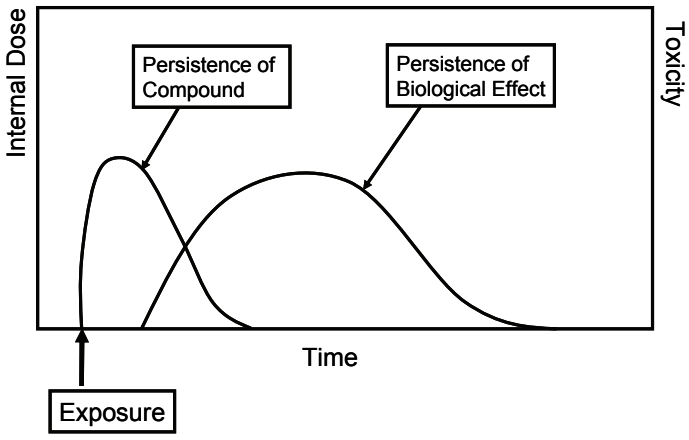


FIGURE 4-5

Conceptual Illustration of Persistence of Mixture Components

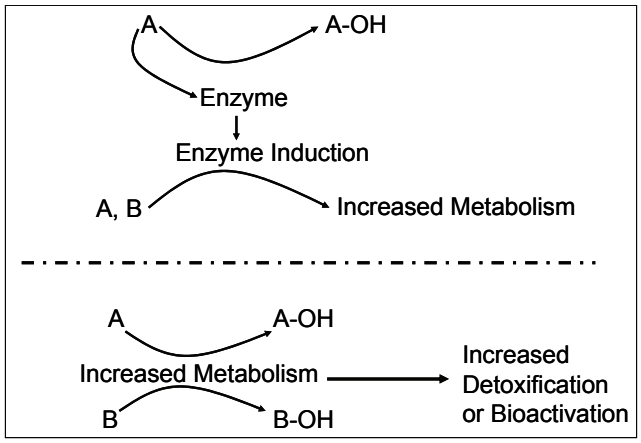


FIGURE 4-6

Conceptual Illustration of Effects of Metabolism on Toxicity

The timing of compound exposure and the duration of biological effects is to 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 3-11). Tumors are not produced when the sequence of the exposures is reversed. This is due to the short biological residence time of TPA (compared to B[a]P) and the short biological persistence of TPA's effects. Mehendale and colleagues provide another example of the biological effects persisting beyond chemical residence time (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 is summarized and considered as the toxicity assessment proceeds through the evaluation of chemical interactions.

4.3.1. Use of Internal Doses in the Hazard Index. Internal dose measurements are becoming more common in chemical mixtures risk assessment and have been applied in the calculation of the HI and to investigate the potential for pharmacokinetic interactions among the chemical constituents (Haddad et al., 1999, 2001). In Haddad et al. (2001), the authors use PBPK models to calculate an interaction-based HI using tissue doses that account for "multiple pharmacokinetic interactions occurring among the mixture constituents." The equation used for a mixture of *n* chemicals is:

$$HI_{Interaction-based} = \sum_{i=1}^{n} TM_i / TR_i \qquad (4\text{-}4)$$

where:

TM_i = tissue dose of the i^{th} mixture constituent estimated by the PBPK model for the human exposure level

TR_i = tissue dose of the i^{th} mixture constituent estimated by the PBPK model for a human "safe level."

The authors compared the interaction-based HI computed for central nervous system effects using Equation 4-4 with the conventional HI (computed using internal doses) over a range of exposure concentrations for different mixtures of dichloromethane, benzene, toluene, ethylbenzene and m-xylene, showing greater than additive effects at the higher total dose levels of the mixture. Such uses of PBPK models can improve the way chemical mixture risk assessments are conducted.

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). This chapter begins with those rough exposure groupings and further evaluates them to form revised groups based on toxicological similarity based on common mode of action or, in cases where data are sparse, on common target organ. A systematic approach is presented to evaluate these chemical 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 4-7a, 4-7b, 4-7c and 4-7d outline a process for classifying chemicals into groups suitable for analysis and then applying the methods shown in Figures 4-2a and 4-2b. These steps are

1) Figure 4-7a (same as Text Box 3-10) – 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 4-7b – 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 toxicological 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. Note that common toxic mode of action is the preferred way to categorize chemicals into groups for analysis of combined toxicity. However, when such data are not available, common target organs can be used, but with less confidence in the results. A discussion of the data and decisions used to group chemicals is included in the risk characterization.
3) Figures 4-7c and 4-7d – Assess the toxic potential of the chemicals/whole mixtures of concern using methods in Figures 4-2a and 4-2b. Figure 4-7c shows a flow chart that first evaluates the whole mixtures and single chemicals for toxicity potential, ensuring that those with the greatest potential to cause toxicity are maintained in the cumulative risk assessment. Then, the chemical groups formed in Figure 4-7b are evaluated for joint toxicity, addressing multiple effects, interactions and exposure routes; these groups are then screened into or out of the cumulative risk assessment. Figure 4-7d provides additional detail on the processes shown in Figure 4-7c, indicating the methods and outputs from this data analysis.

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

FIGURE 4-7a
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
Chemicals in Exposure Groups (Above) Further Grouped Based on Similar Toxicity				
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 4-7b

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 are retained for assessment if information exists on their toxicological interactions.

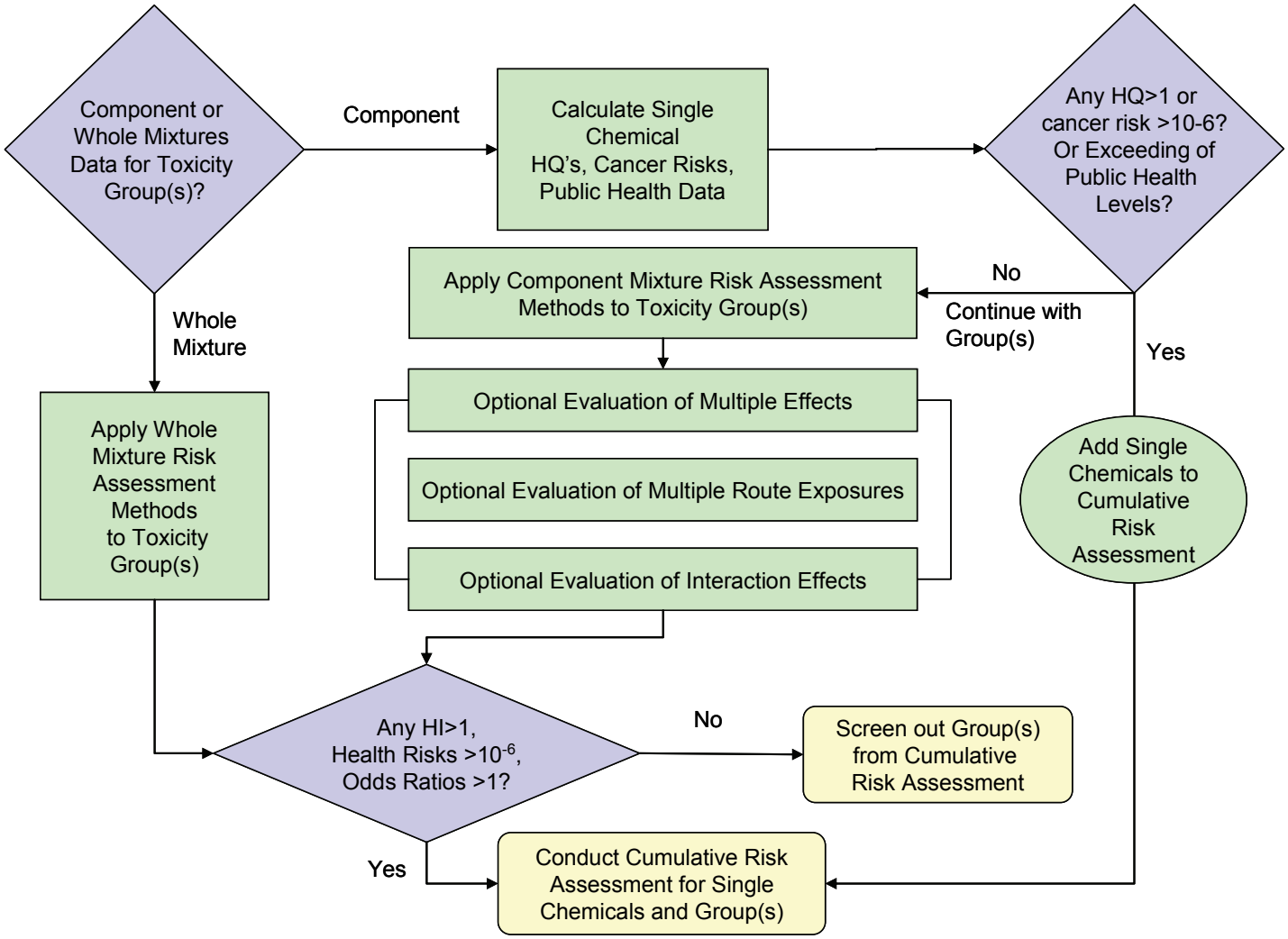


FIGURE 4-7c

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.

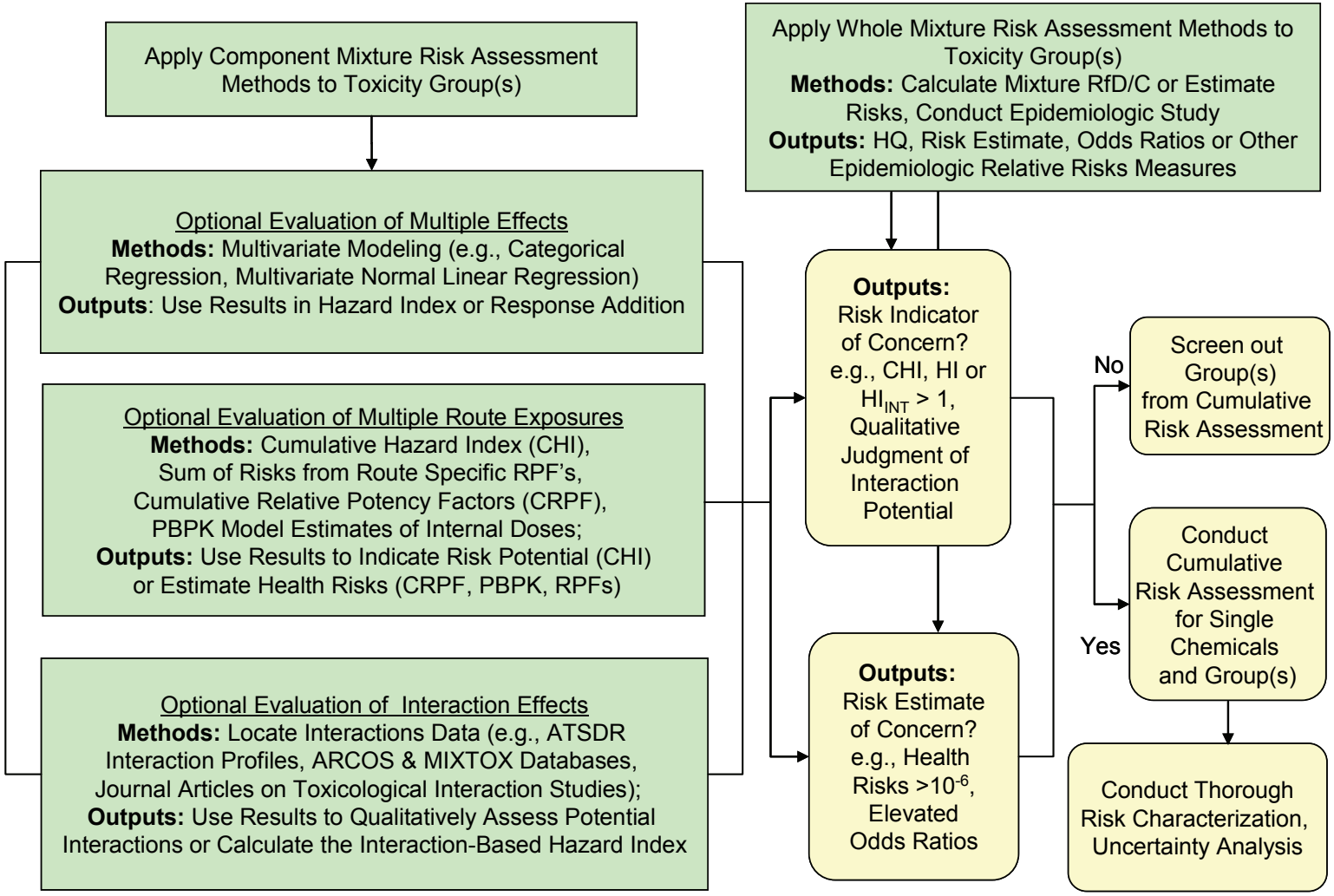


FIGURE 4-7d

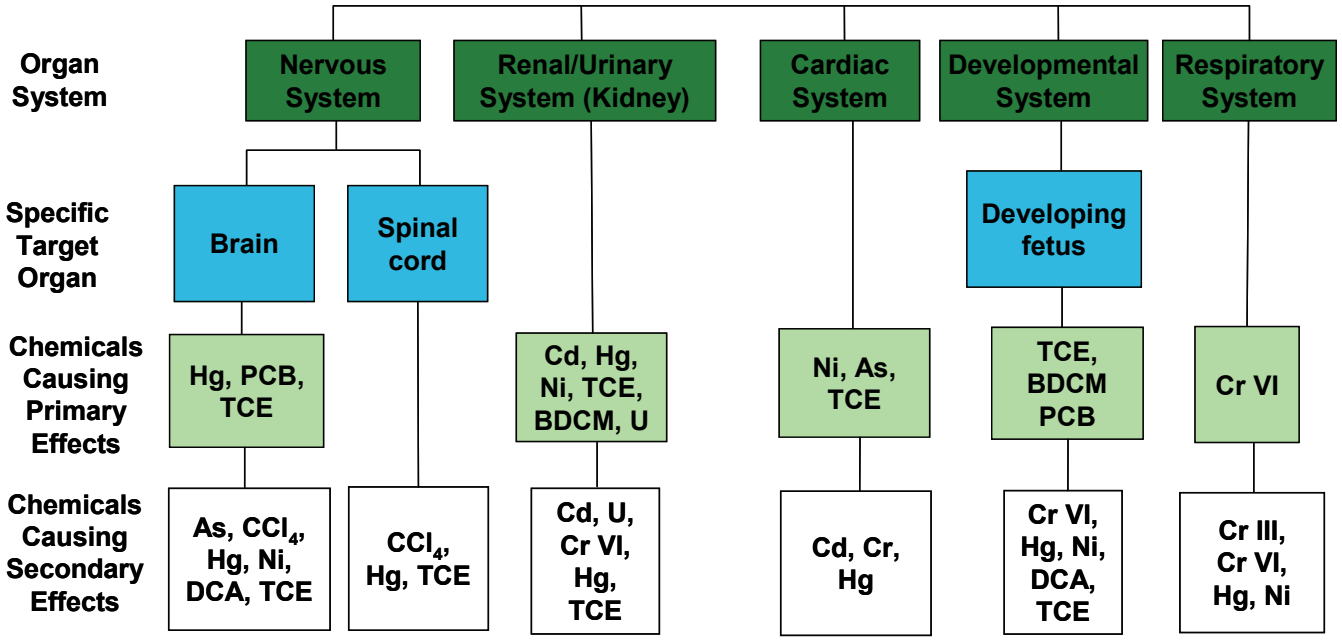
Grouping Chemicals for Cumulative Risk Assessment (cont). Specific mixture risk methods are applied depending on which multiples are being evaluated, with "concern" judged by the appropriate screening value as determined during the Problem Formulation phase of cumulative risk assessment.

4.4.1. Chemical Groupings by Common Effects. The groupings developed in the exposure analysis (Figure 4-7a) categorize multiple chemicals into groups comprised roughly of exposures in the same or different media at the same or different exposure 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 4-7b shows that for each media/time combination, the occurring chemicals are grouped by common target organ or effect, which does not necessarily imply a common toxic mechanism or MOA. 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 4-7b). 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 EPA toxicity information beyond IRIS values for use in the cumulative toxicity assessment.)

An example of the grouping process can be seen using the information shown in Figures 4-8 and 4-9. In Figure 4-8, 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 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: effects mediated by chemical metabolites, effects that follow from chemical insult but do not result in adversity (e.g., enzyme induction), or adverse effects that occur at doses higher than those producing the critical effect.

Target Organ Toxicity Doses (TTDs)
(Text Box 4-2)

The EPA's IRIS database generally derives an oral RfD based on a single critical effect (i.e., the first adverse effect, or its known precursor, that occurs to the most sensitive species as the dose rate of an agent increases) for a single chemical. Thus, cumulative toxicity assessments using secondary effects require the development of additional dose response information beyond readily available EPA values. EPA (2000a) suggests the development of 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). At this point in time, the TTD methodology has only been proposed for noncancer endpoints and for oral exposures. TTDs can then be used in HI 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.



Sources:

- **Municipal Waste Combustor: Hg, Cd**
- **Fish Consumption: Hg, PCB**
- **Drinking Water Disinfection By-Products (DBPs): BDCM, DCA**
- **Source Water Contaminants: TCE, Ni, As, CCl_4, Cr**
- **Contaminated Groundwater: U**
- **Temporary Combustor for Site Remediation: Cd, Cr, Ni**

As = Arsenic (inorganic)
BDCM = Bromodichloromethane
Cd = Cadmium
CCl_4 = 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 4-8

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 sources)

	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
Chemicals in Exposure Groups (Above) Further Grouped Based on Similar Toxicity				
Kidney	Hg, Cd, BDCM	Ni, TCE, U, Cr	Hg, BDCM	Cd, Ni, TCE, Cr
Brain	Hg, DCA	TCE, As, Ni, CCl_4	Hg, DCA, PCB	TCE, As, Ni, CCl_4
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 4-9

Hypothetical Example of Chemical Groupings by Co-occurrence in Media and Time, Similar Toxicity

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 4-9, 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 4-9 are developed by distributing the chemicals associated with the hypothetical exposure sources (Figure 4-8) 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 DBPs 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 are 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 are 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 are considered:

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

  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 is then discussed in the Risk Characterization phase.

- 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 4-9, 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 4-9, 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 it cannot be determined whether or not TCE would still be present or instead be completely metabolized, it may be reasonable to also retain TCE in the risk assessment, but this uncertainty is then 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 Cd and TCE on the cardiovascular system may be based on direct interactions in the heart itself, and by additional, indirect, effects of Cd and TCE on kidney function related to blood pressure regulation. Both TCE and Cd are readily absorbed into the body. TCE is eliminated from the body with a half-life measured in hours, whereas Cd is eliminated from the body with a half-life measured in decades; thus an earlier exposure to Cd may result in persistent body burdens, and internal co-exposure with TCE in tissues. The tissue concentrations and the effects of Cd 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 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 4-10 illustrates a few of the changes (not comprehensive) that would be made in Figure 4-9 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 analyst can move forward to conducting the cumulative toxicity assessment.

4.4.2.1. Uncertainties and Data Gaps in Grouping Chemicals — The amount of data needed for grouping chemicals and analyzing risks for cumulative risk assessment may be significant, particularly when multiple toxic effects and exposure routes are of concern. However, lack of data for certain chemicals or exposure durations is not unique to cumulative risk assessment. Furthermore, uncertainty due to extrapolations (e.g., from animals to humans), potential variability in response due to differential susceptibility of some individuals or subgroups, and knowledge gaps, are incorporated into IRIS or other (e.g., AEGL) reference value determinations. Options for addressing uncertainties associated with extant toxicity values as well as uncertainties associated with lack of toxicity values for key chemicals (i.e., data gaps) are similar to those used in site risk assessments conducted under existing guidance. EPA (e.g., U.S. EPA, 1989a), NRC (e.g., NRC, 1994) and OMB (2006) clearly state the importance of providing a full and open discussion of uncertainties in a risk assessment, including identification of the sources and magnitude of uncertainty associated with the risk estimates. For chemicals that are critical to an analysis, EPA (or other agencies) can be asked to develop toxicity values for the route of exposure(s) and exposure duration(s) of interest. For cumulative assessments, it is also important to assess secondary effects, i.e., those seen at doses above that producing the critical effect on which the standard toxicity value is based. Toxicity values can be derived if the underlying toxicity studies needed to complete the evaluation are available. In the absence of an adequate toxicological database, expert judgment may be used, along with quantitative structure activity analysis, with associated identification and characterization of uncertainty. Finally, as a long range strategy, chemicals may be prioritized for toxicological testing.

4.4.3. Cumulative Toxicity Assessment Scheme. After the joint exposure and target organ groups are determined, the toxicity assessment for each group can then follow the schematic shown in Figure 4-7c. This flow chart begins in the same way as Figure 4-2a and 4-2b in that the risk analyst examines the available data for toxicity 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
Exposure-Toxicity Groups Refined Based on Interactions, Metabolites, Exposure Routes				
Kidney	Hg, Cd, BDCM	TCE, Ni, U, Cr, CCl_4[a]	Hg, BDCM	Cd, TCE, Ni, Cr, CCl_4[a]
Brain	Hg[b]	TCE, As, Ni, CCl_4, DCA[c]	Hg, DCA, PCB	TCE, As, Ni, CCl_4, DCA[c]
Fetus	Hg, BDCM[b]	TCE, Ni, Cr, CCl_4[a], DCA[c]	Hg, BDCM, DCA, PCB	TCE, Ni, Cr, CCl_4[a], DCA[c]
Heart	Hg, Cd	TCE, Ni, As, Cr, CCl_4[a]	Hg	Cd, TCE, Ni, As,Cr, CCl_4[a]
Lung	Hg	Ni, Cr	Hg	Ni, Cr

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

FIGURE 4-10
Examples of Toxicity Group Refinements

on the whole mixture and on the mixture components. The whole mixtures and single chemicals are first evaluated for toxicity potential; those with the greatest potential to cause toxicity are maintained in the cumulative risk assessment. The whole mixtures may be evaluated according to the methods in Figure 4-2a (Section 4.3.3.1). Then, for the toxicity groups in Figure 4-9, 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 Figure 4-2b for evaluation of component data. Initially, 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. Public health levels for these chemicals are also collected and checked against environmental levels. If calculations show any HQ >1 or cancer risk $>10^{-6}$ or if a public health level is exceeded, then that single chemical is designated to remain in the cumulative toxicity assessment. (It is not removed from the toxicity group.) The next step is to apply the component-based chemical mixture risk assessment methods (flow chart in Figure 4-2b) to each toxicity group, using the HI (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 toxicological similarity of the component chemicals (see U.S. EPA, 2000a, for details on applying these methods). Finally, the optional quantitative methods detailed in Figure 4-7d may be undertaken to evaluate multiple effects (Section 4.5), toxicological 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 qualitative 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, cancer risks or public health levels, as well as any whole mixtures that may have the potential to cause toxicity and finalizes the cumulative risk assessment, including a complete Risk Characterization (Chapter 5).

4.4.3.1. Evaluation of Whole Mixtures Data—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 as shown in Figure 4-2a (see procedure in Text Box 4-3) and compared with environmental

exposure levels. For example, an RfD 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 4-11. 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 4-7c, if the whole mixture toxicity is shown to be of concern, then it remains 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)

4.4.4. Evaluating Subpopulations. Information on vulnerable subpopulations may be collected and included in the cumulative risk assessment when such information is available. An extensive treatment of how to incorporate such information into the cumulative risk assessment will not be described in this report, but future research on this aspect of cumulative risk assessment may contribute insights and is encouraged. The Agricultural Health Study and other literature on mixture exposures and potential susceptibilities related to environmental exposures (see Chapter 1) will become useful data sources in the future 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 may be evaluated (Chapter 2). In order to conduct an initial evaluation of the subpopulation health impacts, chemical mixture exposure and risk estimates for vulnerable subpopulations may 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 is broadened to include factors beyond those considered for single chemicals. An important difference between cumulative risk assessment and traditional single-chemical assessments is the

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 4-11
Complex Mixture Reference Dose

number of health effects evaluated. In the assessment of chemical mixtures, secondary health effects may be observed as a result of combined chemical exposures that are different in phenotype or magnitude from the critical (primary) effects caused by the chemicals individually. These secondary health effects may occur at doses or exposures higher than those causing the critical effect. Conversely, observed toxic threshold(s) or effect level(s) (e.g., a LOAEL) for single chemicals may be altered such that the dose(s) required to elicit the same and/or additional effect(s) may be less when the exposure is to a mixture (e.g., Nickel causes increased sensitivity to Cobalt-induced dermal allergy). Thus, it is important to evaluate secondary effects for those chemicals to which humans may be exposed in combination. In these cases, the doses of the chemicals in the mixture may act in an additive manner to cause one of these secondary or higher level effects, or the responses (effects or risks) themselves may be additive. In addition, co-exposure to these chemicals may result in toxicological interactions (e.g., synergism or antagonism) related to a secondary or higher level effect. The method described in Figures 4-7a, 4-7b, 4-7c and 4-7d shows that the cumulative risk assessment includes an evaluation of all adverse effects, as evidenced by available health effects data (e.g., toxicology data, public health data and epidemiology studies). Finally, the set of identified effects takes 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 concentrations (exposures) used to develop toxicity data in test animals. When external exposure levels are used in the risk assessment, then inferences about multiple effects may be highly uncertain. When data are available and resources permit a more extensive investigation, internal chemical doses may be developed or inferred from pharmacokinetic and mechanistic information. The issue of whether to express exposure in external or internal terms becomes important when the relationship between exposure concentration and internal concentrations (tissue dose) is nonlinear or has not been characterized. Another level of complexity can be avoided when internal doses are used to evaluate the response in multiple-organ systems, such as the immune system. Here, tissue concentrations may vary appreciably among the multiple organs involved, and those tissue concentrations may or may not be linearly related to external exposures. Chemicals that affect organs or tissues that are parts of a larger biological system may be considered as affecting the same target system. Finally, exposure to chemical mixtures may result in toxicokinetic alterations in the body that may alter the internal

dosimetry and tissue distribution of chemical components. 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 (HI) and response-addition approaches and a comparison of the results. This approach begins by analyzing dose response relationships for each single chemical and incorporating all toxic effects in the same modeling procedure. Various statistical models could be applied (e.g., multivariate normal linear regression or 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 toxicological judgment will be used to illustrate estimating the probability of a certain severity level of (non-specific) response that can represent a number of different toxic effects, given exposure to a single chemical. From the modeling results, a risk estimate for the exposure of interest can be made for that single chemical, or a benchmark dose (BMD) can be estimated (e.g., a 5% effective dose or ED_{05}). To apply dose addition, this modeling approach is conducted for each of the chemicals in the mixture, and a HI is calculated by summing the ratios of each chemical's exposure to its BMD, which provides an indication of risk for the mixture. To apply response addition, the categorical regression model can be used to predict the risk of an adverse effect for each individual chemical at its environmental exposure level; these risk estimates can then be summed across chemicals to calculate the mixture risk. These results can be compared in the Risk Characterization phase (see Chapter 5) to evaluate the potential health impacts for the exposure scenario of interest.

Ordinal categorical regression is a statistical modeling procedure that allows for a dose-response assessment of several toxicological 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 (Dourson et al., 1997; Farland and Dourson, 1992; Guth et al., 1991; Rao et al., 1993; 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 (see Appendix C for further discussion of severity of toxic effect). 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 EPA's 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.

To illustrate the modeling procedure, an example is shown here from Dourson et al. (1997), where categorical regression analysis was used to model human clinical data to describe the relationship between the logarithm of doses and severity levels of cholinesterase inhibition for the pesticide, aldicarb. Table 4-2 shows the four, ordered categories of toxic severity for cholinesterase data that were used to classify the response data, along with the clinical effects expected to be observed at each severity level. In Dourson et al. (1997), results from two human clinical studies available on aldicarb, Haines (1971) and Wyld et al. (1992), were evaluated using the criteria in Table 4-2, and each subject was placed in a severity category as summarized in Table 4-3. Both studies had similar experimental designs (see summaries in Dourson et al, 1997). A categorical regression model was developed to predict the probability that a subject would exhibit a certain severity level of cholinesterase inhibition, given the exposure dose.

In the catergorical regression model, the toxic response was related to the explanatory variable, logdose, using a logistic function and *P* was defined as the probability of observing a response of a certain severity or *a lesser response*. The logistic function used to express the relationship between *P* and the explanatory variable, dose, is given below:

$$Log\left(\frac{P(s \le i)}{1 - P(s \le i)}\right) = \alpha_i + \beta * D \qquad (4\text{-}5)$$

TABLE 4-2

Severity Assignments for Cholinesterase Inhibition Data
(Adapted from Dourson et al. ,1997)

Severity Category	Site	Effect
4 Frank Effects	Cholinergic effects	Severe abdominal pain, nausea and/or vomiting, diarrhea
	Cholinergic effects	Seizures, severe disorientation or confusion, excitation
	Whole Body	Mortality
3 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
2 Non-Adverse Effects	Plasma, whole blood or RBC acetylcholinesterase	Inhibition (e.g., observed, but less than 20%)
1 No Effects	All	No effect

TABLE 4-3

Frequency of Categories of Effect Associated with Aldicarb Exposure in Humans
(Adapted from Dourson et al. ,1997)

Study	Dose (mg/kg/day)	Group Size	Frequency of Responders within Categories of*			
			No Effects	Non-adverse Effects	Adverse Effects	Frank Effects
Haines, 1971	0.025	4	0	0	4	0
	0.050	4	0	0	4	0
	0.10	4	0	0	2	2
Wyld et al., 1992	0.0	22	22	0	0	0
	0.010	8	8	0	0	0
	0.025	12	2	9	1	0
	0.050	12	0	9	3	0
	0.075	4	0	0	4	0

*Numbers reflect a judgment that whole blood (Haines, 1971) or red blood cell (Wyld et al., 1992) cholinesterase inhibition of 20% or greater is considered an adverse effect. This percentage can be debated and is a source of uncertainty for the analysis.

where:

P = the probability of observing an effect of severity i or less,
s = the severity of the effect,
i = the severity category 0, 1, 2 or 3,
α_i = an unknown intercept parameter associated with severity i,
β = an unknown slope parameter associated with the dose,
D = the logdose of the chemical, aldicarb.

Table 4-4 shows the results of the regression modeling. Using the values in this table and rounding down, a hypothetical example of a 10% BMD level for use in developing a HQ (and subsequently using this in a HI calculation) would be roughly equal to 0.02 mg/kg. (It may be noted that a lower bound on the BMD, a BMDL, would typically be used in the HQ calculation, but these values are not shown in Dourson et al. [1997]; thus the BMD is used here for illustration.) Alternatively, if a hypothetical exposure in a community were equal to 0.01 mg/kg, then the upper bound human risk of ~4% in the table could be used in a response addition calculation for that risk assessment.

This categorical regression procedure can be expanded beyond a single group of toxic effects to include other effects whose severity is judged to be of a similar nature and level (e.g., Table 4-2 could be expanded to include severity judgments for liver and kidney effects along with cholinesterase inhibition). In addition, duration can be included as a second dependent variable in the model. Using this procedure, the dose-response relationship for multiple effects can be modeled and shown as the probability 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 resulting equation for the multiple effects HI, for chemicals k = 1, 2,…,n, and exposures E_k, would be:

$$HI(effects) = \sum_{k=1}^{n} \left(\frac{E_k}{BMDL_k / UF_k} \right) \qquad (4\text{-}6)$$

TABLE 4-4

Modeled Probabilities of an Adverse or Frank Effect

Dose (mg/kg)	Inhibition >20% = Adverse Effect	
	Mean P(AE or FE)*	Upper 95%CL On P(AE or FE)*
0.001	--------	0.00001
0.003	--------	0.0007
0.01	0.0014	0.04
0.015	0.03	0.17
0.02	0.14	0.36
0.025	0.44	0.67
0.03	0.79	0.93
0.035	0.89	0.97
0.04	0.95	0.99
0.10	0.99	1.00

*P(AE or FE) is equal to P(s $\geq$ 3), i.e., the probability of observing an adverse effect (severity level 3) or a frank effect (severity level 4), given dose. P(AE or FE) is also equal to 1 – P(s $\leq$ 2), i.e., one minus the probability of observing a non-adverse effect or no effect.

As an example, suppose chemical A and chemical B are in a mixture with exposures doses of 8 and 2 mg/kg, respectively. From their individual categorical regression models of multiple effects, the 10% BMDL's are estimated at 50 and 75 mg/kg, respectively. It is determined that an UF = 100 is appropriate for each chemical. Therefore, the HI(effects) = 8/(50/100) + 2/(75/100) = 16 + 2.7 = ~19, which would indicate potential risk for adverse effects at that environmental exposure.

A probabilistic mixtures risk estimate could also be calculated for multiple effects using the categorical regression results. Based on Equation 4-2 (and expanding for more than k = 1,..,n chemicals), 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:

$$R_m(effects) = 1 - \prod_{k=1}^{n} P_k(severity \leq 2) \qquad (4\text{-}7)$$

where P_k(severity $\leq$ 2) is the same as P(s $\leq$ i) when i = 2, in Equation 4-5 above. These probabilities can be calculated from the regression modeling results. As an example using some of the data from Table 4-4, the mean P(s $\leq$ 2) for a dose of 0.015 mg/kg = 1 – P(s $\geq$ 3) = 1 – 0.03 = 0.97. Suppose another chemical present in the mixture is measured at a exposure dose of 0.04 mg/kg and that its categorical regression model evaluated at that dose yields the P(s $\leq$ 2) = 0.99. Then, using Equation 4-7 for that two chemical mixture, R_m(effects) = 1 – (0.97)*(0.99) = 1 – 0.96 = 0.04, the risk estimate for multiple effects for the mixture exposure of interest.

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 may 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, expert judgment of the toxicological significance is used 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 are 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

TABLE 4-5

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).

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

EPA (2000a) defines toxicological interactions as any toxic responses that are greater than or less than what is observed under an assumption of *additivity* (e.g., a departure from dose additivity or response additivity for a group of chemicals). 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 toxicological judgment to statistical determinations. For cumulative risk assessment, interactions information may be collected from the toxicological and epidemiologic literature and used to inform the grouping process. EPA has two collections of bibliographic summaries of interaction studies: the Integral Search System (Arcos et al., 1988) and the MIXTOX database (Marnicio et al., 1991). ATSDR has also published eleven interaction profiles for common environmental contaminants (ATSDR, 2006; Pohl et al., 2003). For example, in Table 4-5, the non-additive interactions are shown for four metals: As, Cd, Cr and Pb (ATSDR, 2004). As Table 4-5 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, toxicological 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 4-7b), those chemicals are 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) or by evaluating interactions using an internal dose HI (Section 4.3.1).

4.6.1. Toxicology of Interactions. A mixture can consist of chemicals that cause a unique toxicological expression that was not anticipated from the toxicity of the individual compounds; the toxicodynamic process of one compound influences that of another (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. TD processes include 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, toxicological interaction among compounds may be direct or indirect. 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. Direct interactions are 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 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 is 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).

It is important to carefully evaluate information on acute toxicities. 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. 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, it is useful to consider the severity of the underlying effect (e.g., cytotoxicity and cellular regeneration). For compounds that must be metabolized to be tumorigenic, TK interactions at the enzyme level are an important aspect to be evaluated. For additional details on TK and TD interactions, see Appendix C of U.S. EPA (2000a [Mixtures Guidance]).

4.6.2. A Quantitative Method for Evaluating Interaction Effects. To account for chemical interactions in a site assessment, EPA recommends applying the 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 toxicological 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 below is the additive HI and the second summation shown below is the modification for interactions, the formula for the HI_{INT} is:

$$HI_{INT} = \sum_{j=1}^{n} HQ_j \sum_{k \neq j}^{n} f_{jk} M_{jk}^{\,B_{jk} g_{jk}} \tag{4-8}$$

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:

$$f_{jk} = \frac{HQ_k}{\left[\sum_{j=1}^{n} HQ_j\right] - HQ_j} \tag{4-9}$$

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

B_{jk} = score for the WOE that chemical *k* will influence the toxicity of chemical *j*. To calculate, the formula is:

$$g_{jk} = \frac{\sqrt{HQ_j * HQ_k}}{\left(HQ_j + HQ_k\right)/2} \quad (4\text{-}10)$$

g_{jk} = degree to which chemicals *k* and *j* are present in equitoxic amounts.

The current WOE classification and scores are given in Table 4-6 (U.S. EPA, 2000a). This scheme does not specifically focus 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 the 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 does not have to be the same for the influence of chemical *j* on the toxicity of chemical *k*; i.e., $B_{jk} \neq B_{kj}$. The WOE determination begins with a classification of the available information, followed by a conversion of that classification into a numerical weight.

The term M_{jk} represents the maximum interaction effect that chemical *j* can have on the toxicity of chemical k. As with the WOE score, the interaction magnitude need not be symmetric; i.e., the magnitude of interactive influence of chemical *k* on the toxicity of chemical *j* may be different than the corresponding magnitude of chemical *j* on the toxicity of chemical *k*. When binary mixture toxicological data are available, a simple calculation can be used to determine a value for M_{jk} from Effective Doses (e.g., from ED_{10}'s that cause a 10% effect in the test animals). EPA uses the proportional change in effective dose as the interaction magnitude. For example, if the ED_{10} is predicted to be 20 mg/kg/day for chemicals *j* and *k* together under an assumption of dose addition, but the observed experimental value for *j* and *k* together is equal to 5 mg/kg/day, then the interaction magnitude would equal 20/5 = 4. In the absence of data, U.S. EPA (2000a) recommends a default value of 5 based on observations of interactions data from the literature.

This method for modifying the HI is based on commonly discussed principles of toxicological interactions. The algorithm, however, does not attempt to directly model toxicological interaction mechanisms. While the interaction magnitude is based on directly observed toxicity measures, the adjustment for different component doses is

TABLE 4-6

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

Source: U.S. EPA (2000a).

simple and heuristic. Instead of estimating joint toxicity or risk, the interaction HI method models "concern" for toxicological interactions, which reflects issues of magnitude as well as likelihood. In this respect, the interaction HI is interpreted the same way as is the common additive HI; the approach corresponds more closely with the current use of uncertainty factors in the risk assessment of single chemicals than with an attempt to biologically model interactions. As more interaction studies are completed and more interaction mechanisms and modes of interaction are understood, this method for modifying the HI will be further refined.

4.7. EVALUATING MULTIPLE ROUTE EXPOSURES

A cumulative risk assessment considers exposures 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 decides 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 PBPK 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 describes the uses of route-to-route

EPA Uses of Route to Route Extrapolations U.S. EPA (2003g) 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 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 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 equal to oral absorption. Air concentration estimates for human exposure 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.

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 analysts to sum HQs (Equation 4-1) and cancer risks (Equation 4-3) 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 5.5.1.) Although there is no discussion of summing across exposure routes and pathways in the U.S. EPA (1986b, 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 online on its Web site (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 4-10. Further discussion of this approach is given in Section 5.5.1 in terms of a cumulative hazard index (CHI), 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 4-12 graphically illustrates the process to be followed in developing an RPF assessment. 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

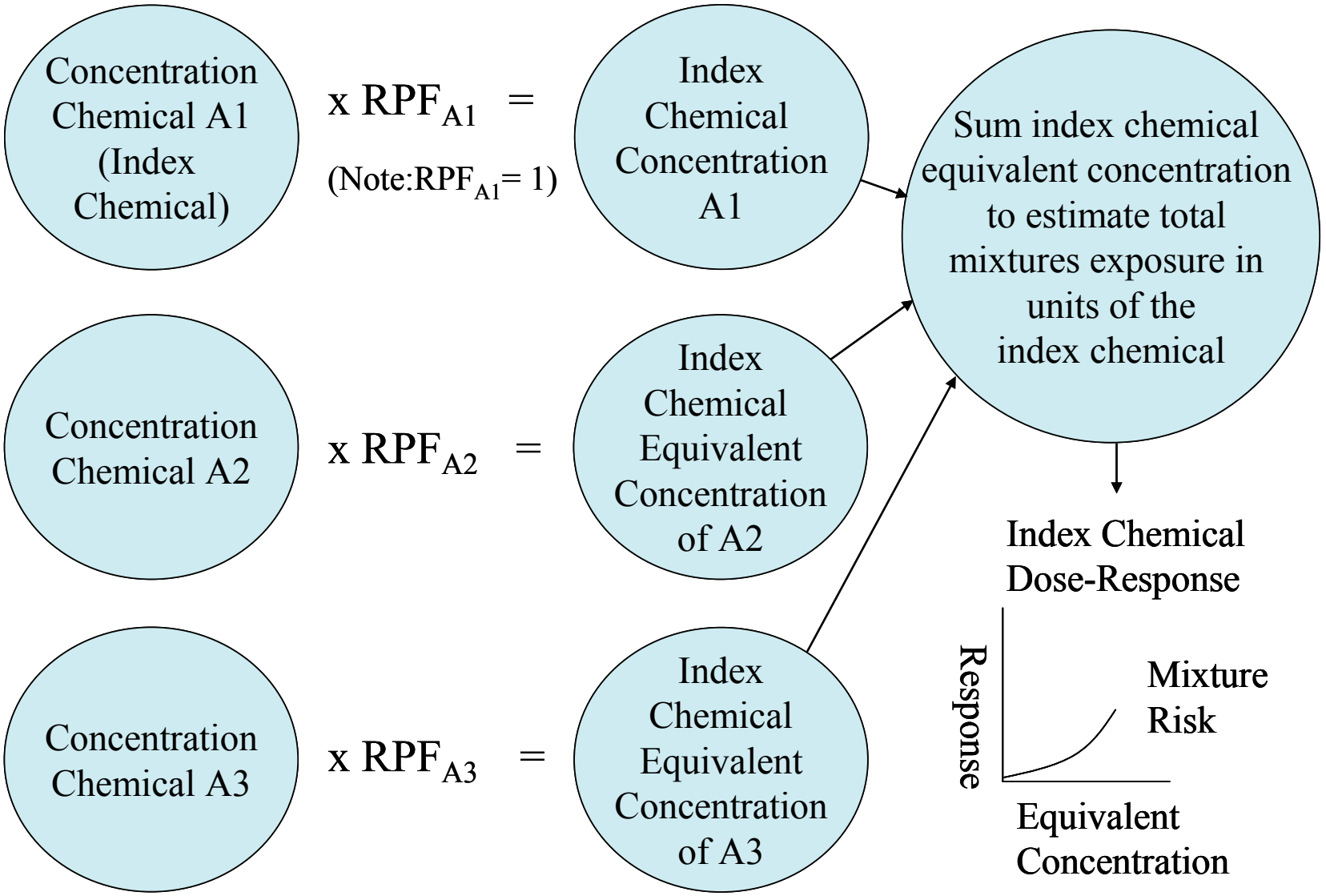


FIGURE 4-12
Schematic for Relative Potency Factor Approach

express the total mixture dose in terms of an Index Chemical Equivalent Dose (ICED).[5] 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 toxicological dose-response data set (U.S. EPA, 2000a). 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.

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 4-13 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 4-10). Using two exposure routes, inhalation and oral, Figure 4-13 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 the ICED for the mixture is calculated using the RPF approach (U.S. EPA, 2000a). (Note the text here will only refer to an ICED. However, for clarity in

[5] 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.

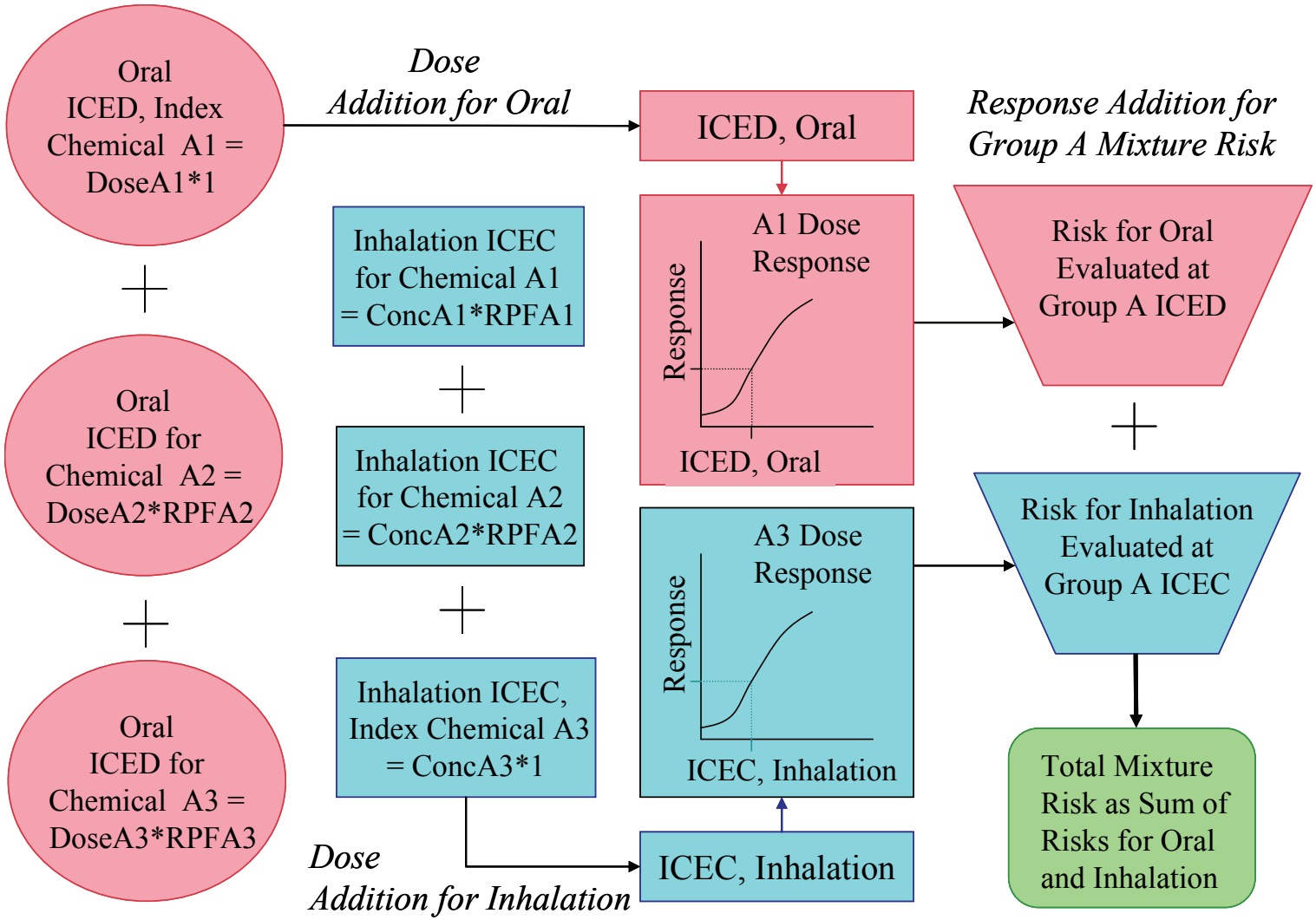


FIGURE 4-13

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

Figure 4-13, 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) 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.

EPA has proposed the RPF approach as a means 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 toxicological data are needed for at least one component of the mixture that can be used as the index chemical. Scientific judgment and analysis of available data are used to assess the relative toxicity of 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 toxicological 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 for applying 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, for the risk analyst to identify any studies or dose-response data on the multi-route mixture exposure that can support (refute) 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, 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 pharmacokinetic 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, 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 of the Risk Analysis phase 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 may be supported by toxicity arguments that are relevant to the estimated exposures. When such information is weak or inconclusive, the chemicals and pathways are retained in the assessment.

5. CUMULATIVE RISK CHARACTERIZATION

The last phase of cumulative risk assessment, Risk Characterization, assembles all the information from the Risk Analysis phase and interprets the results in the context of the problem(s) formulated in the Planning and Scoping phase. Text Box 5-1 lists some important elements of a Risk Characterization that are useful to consider in a cumulative risk assessment. As described in EPA guidance (U.S. EPA, 2000f), Risk Characterization includes two products:

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

- Results of the integrated analysis
- Quality of and confidence in the available data
- Uncertainty and sensitivity analyses
- Justification of defaults or assumptions
- Related research recommendations
- Contentious issues and extent of scientific consensus
- Effect of alternative assumptions on conclusions and estimates
- Highlights of plausible ranges
- Reasonable alternative models
- Perspectives through analogy

(U.S. EPA, 2000f)

1. **Integrative analysis** - a technical presentation of the predicted risks and uncertainties in an assessment
2. **Risk Characterization summary** - a condensed version of the results and uncertainties that emphasizes the recommendations of the analysis, written in a style that communicates the "bottom lines" to the general public.

The Risk Characterization transparently presents the logic that leads to various technical decisions in the analysis (e.g., those regarding the inclusion or exclusion of specific chemical classes or groups of chemicals, specific exposure pathways and the choice of specific Risk Characterization approaches). The analysis also discusses the support for analytic assumptions offered by data and professional judgment (e.g., assumptions used to group chemicals for use in risk assessment procedures). As discussed in the *Supplementary Mixtures Guidance* (U.S. EPA, 2000a), any quantitative or qualitative risk estimates must be accompanied by the explanation of assumptions made when estimating the risks and uncertainties associated with the risk estimates. These obligations of Risk Characterization apply to all risk assessments conducted by the EPA.

While this discussion focuses on issues to consider in the integrative analysis product, several aspects of the Risk Characterization summary are also discussed. Results of the Risk Characterization may impact various non-technical individuals. The economic and social ramifications of cumulative risk assessments may require that the Risk Characterization results highlight the important issues and uncertainties and explore their implications for different audiences. These stakeholders may be concerned with

- the number of people exposed;
- the range of uncertainty around the exposure and health risk estimate;
- the critical variables driving the assessment, the existence of data gaps;
- the bottom-line conclusion; and
- the degree to which the Risk Characterization results support a regulatory decision.

Section 5.1 presents an overview of Risk Characterization in a cumulative risk assessment. Section 5.2 describes special Risk Characterization concerns of a cumulative Risk Analysis including questions that may be used to further guide the analyst in developing a cumulative Risk Characterization. Section 5.3 presents an approach for developing an integrative assessment for a cumulative risk assessment that includes considerations of multiple chemical exposures through multiple exposure pathways. Section 5.4 discusses potential interaction factors that the analyst may need to consider and Section 5.5 presents summary recommendations. Finally, section 5.6 presents a hypothetical example using the CHI.

5.1. CHARACTERIZATION OF RISK IN A CUMULATIVE RISK ASSESSMENT CONTEXT: AN OVERVIEW

Risk Characterizations of cumulative risk assessments evaluate risks posed to the general population and vulnerable subpopulations. While risk characterizations of cumulative risk assessments include characterization of single chemical risks, these are not the focus of this chapter and are not addressed in detail further. As presented in Chapters 1 and 2, cumulative risk assessments include all steps of the traditional risk assessment paradigm (i.e., hazard identification, dose-response, exposure assessment and risk characterization); however, these steps are expanded beyond the elements pertaining to single chemical assessments to account for the complexities of cumulative risk (U.S. EPA, 2000a, 2003a). Chapters 3 and 4 of this document describe approaches for conducting cumulative risk assessments that include analyses of multiple chemicals, multiple exposure pathways and routes, multiple toxic effects over distinct time frames and joint exposure response relationships. Following these evaluations, the pieces are integrated into an overall conclusion about risk, along with clear descriptions of the analytic limitations and uncertainties (NRC, 1983, 1994).

In the integrative analysis product of the Risk Characterization, the analyst evaluates the collective information and identifies information gaps, uncertainties at the interfaces between different process steps and the appropriateness of the potentially

different levels of analysis across the steps of the risk assessment (uncertainties within the steps of the process likely have already been identified). For example, combining dose-response and exposure data that are collected over different durations of time or at different levels of biological organization necessitates the use of additional assumptions or additional data gathering activities.

The development of the integrative analysis of a cumulative risk assessment is typically an iterative process, where information from each process phase is reconsidered from the perspective of the information generated during the other phases. Chapters 3 and 4 emphasize the iterative nature of the conduct of a cumulative risk assessment. The need for this iterative assessment approach continues in the Risk Characterization. An important iteration is the comparison of analytic results with the goals set out in the Problem Formulation phase. The description of uncertainties plays a pivotal role in determining whether these goals have or, perhaps, can been met. If the results do not sufficiently address the goals, iteration through one or more of the previous steps might be needed, including the initial Planning and Scoping and Problem Formulation.

Considerations of multiple chemicals, multiple exposure pathways and routes, multiple toxic effects over distinct time frames and joint exposure response relationships complicate the characterization of risks. Text Box 5-2 presents examples of this complexity for a hypothetical comparative risk decision that considers cumulative risks. These complications increase the difficulty in understanding the influences of combinations of underlying assumptions on the analytic results and possibly the implications of the assessment results.[1]

5.2. SPECIAL CONCERNS WITH CUMULATIVE RISK CHARACTERIZATION

The EPA guidance documents on Risk Characterization present lists of issues or questions that may be addressed in the integrative analysis step of Risk Characterization. Issues important for single chemical Risk Characterization (e.g., 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) may not be very relevant to the cumulative Risk Characterization. Throughout the analysis, the analysts make decisions that influence the conclusions of the assessment. Such decisions may occur during Planning and Scoping, during the iterative exposure and dose-response analyses and during the integrative analysis in the Risk

[1] These complicating factors also make the successful communication of the uncertainties to both the risk manager and the public in the Risk Characterization summary product difficult.

Characterization. The following list of questions may help to further guide the analyst in developing a cumulative Risk Characterization. It covers most of the issues raised in the Risk Characterization handbook (U.S. EPA, 2000f, Chapter 3).

Overview

- Have the goal(s) of the assessment been met?
- Is the level of the analysis consistent throughout?
- Are the exposure scenarios (including pathways and routes) considered appropriate?
- Are the type(s) of exposure data available, analyzed and used in the Risk Characterization appropriate?
- Are the types of toxicity data available, analyzed and used in the Risk Characterization appropriate?
- Is the choice of methods for evaluating risks posed under the selected exposure scenarios appropriate?

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

Consider a site with soil contamination due to multiple metals and organic compounds where the decision alternatives are open public access or full closure (clay cap and a fence). The risk assessment evaluates the public access scenario. If the risk assessment outcome determined that exposures would likely exceed acceptable risk levels, the risk manager may opt for site closure.

The complications include population-dependent exposure characteristics. For example, the population near the site may include adults and children with quite different exposures. In the risk assessment, children are assumed to be exposed predominantly by direct contact with soil (dermal absorption and ingestion) and adults primarily by inhalation of dust. Groundwater, contaminated from gradual migration through the soil, is a source of drinking water for some adults and children. This is predicted to result in ingestion route exposures to relatively low pollutant concentrations.

Complexities to Consider when Evaluating Cumulative Risk

- Different proportions of chemicals in inhaled dust compared with ingested groundwater, leading to different critical effects and different toxicological interactions
- Different toxic sensitivities of adults versus children
- Time-varying combined exposure from soil and groundwater that reflects multiple routes as well as timeframes
- Background exposures to pollutants exhibiting similar patterns of toxicity
- Population vulnerabilities.

The integrative analysis may evaluate the relative impact of each of these complexities on the cumulative risk estimates. Any joint contributions to risk may 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)
- Based on mixtures risk assessment methods (See Chapter 4), predictions of adult risk and child risk for multiple chemicals for all routes combined and over different exposure routes and timeframes
- Quality of the multiroute exposure
- 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-end exposure (for adult and for child) and the ranking of the most influential factors driving the risk estimates (a quantitative sensitivity analysis if possible).

To Address Multiple Chemical Exposures, Health Effects and Time Scales

- 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?
- Are the spatial scope and temporal scale of the analysis consistent across analytic components?
- 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 to the predicted health effects?
- 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 phase of the assessment process
- If a health effect was the initiating factor or impetus for the cumulative risk assessment, is that effect adequately addressed in the Risk Characterization?
- Are the population vulnerabilities clearly described?

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 or their exposure-related behaviors 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?

To Address the Initiating Factor

Elevated Health Effects

- Are the health effects that initiated the analysis actually elevated in the community?
- Are populations in the group differentially affected?
- Are the effects adequately addressed in the Risk Characterization?
- Has the Risk Characterization identified potential cause(s) of the health effects?
- Has a causal analysis been undertaken in the context of the cumulative risk assessment?
- Does the Risk Characterization adequately address epidemiologic concepts of causation (e.g., Hill, 1965; Susser, 1991) or those from evidence-based toxicology (e.g., Guzelian et al., 2005)?
- If the assessment did not identify a specific causal agent or agents, but has determined that the population is experiencing an increased incidence of an

adverse health effect(s) (i.e., incidence significantly above normal background), does the risk characterization adequately describe the exposures to the contaminants evaluated and the reasons that they are unlikely to be causing the health effect?

- Has the Risk Characterization adequately described the types of studies needed if the causal agents can not be identified?

Elevated Concentrations

- Are the environmental concentrations or biomonitoring data that initiated the analysis actually elevated in the community?
- Are the potential health effects of such elevations adequately addressed in the Risk Characterization (e.g., Guzelian et al., 2005)?
- Is there evidence that the effects anticipated by the toxicology data are actually being observed in the community?
- Has the Risk Characterization identified potential source(s) of the pollutants that are elevated?
- If the Risk Characterization cannot identify a specific source(s) but has determined that the concentrations are elevated, has the study adequately described the evaluation of potential sources of such contaminants in the community? (A description of the evaluation of potential sources that are not considered to be contributing to the elevated concentrations may aid future investigations).
- If the initiating factor was elevated environmental concentrations, has the Risk Characterization adequately described the likely exposure pathways for the population and adequately characterized the risks posed by the elevated concentrations? Have the spatial and temporal aspects of these analyses been fully characterized?
- If the initiating factor was biomonitoring data, have the likely exposure pathways and routes been identified?
- Has the Risk Characterization adequately characterized the types of risks associated with the effects and described the types of health studies needed in the population?

Multiple Sources

- Have the quantities of chemicals released from the multiple sources that initiated the analysis been adequately characterized?
- Does evidence show that exposure pathways to vulnerable subpopulations are complete?
- Are there other potential sources of the chemicals in the community? Has the environmental fate of the released chemicals been adequately evaluated?

- Have the exposure assessment and the toxicity assessment been adequately conducted?
- Has the Risk Characterization adequately integrated the exposure assessment and dose response assessment?
- Has the Risk Characterization characterized the types of risks associated with the chemicals and described the types of health studies needed in the population?

It is important to clearly summarize the logic (e.g., quality of the supporting data) underlying each of the responses to each relevant question to ensure transparency and clarity of the assessment's conclusions. When possible, for each of the assumptions, the impact of alternative choices on the resulting risk estimates may be described (e.g., a sensitivity analysis) (see Section 5.3). For example, if an exposure pathway is screened out because adequate data are unlikely to be obtained, then it is useful to describe the impact of ignoring that pathway in the integrative analysis (i.e., even if the analyst identifies the direction of potential error; e.g., exclusion of an exposure route is likely to underestimate the risk slightly because actual exposures to the mixture will then be slightly higher than those predicted via the routes considered.).

The level of analysis can vary across assessments. The Risk Characterization discusses whether the analysis was conducted at a screening level or a refined level, clearly identifying assumptions employed and whether they are consistent with the stated analytic level. Screening level assessments typically employ many simplifying assumptions. In a cumulative Risk Analysis, these could include conservative grouping practices. Chemical grouping into environmental fate groups or health effects groups could be based on crude criteria in a screening level analysis (e.g., all chemicals affecting cancer could be included in a single health group in a screening analysis and the cancer risks associated with such exposures could be estimated using response addition). Screening level assessments also typically employ steady-state environmental fate and exposure models; they also may employ deterministic model variables (e.g., a single high-end exposure factor value, such as all members of the population consume 2 L of drinking water each day). Refined analyses may employ fewer assumptions than screening analyses. Chemical groupings may be based on sophisticated measures (e.g., health effects grouping may be based on MOA analyses). Dynamic models of environmental fate may be employed in a refined modeling analysis. Exposure models may include additional temporal or spatial resolution and may be based on probabilistic analyses. While the level of analysis may be described in the integrative analysis, these distinctions may be included in explanations of how the

results of the assessment are interpreted and used in the Risk Characterization summary.

An important aspect of cumulative risk assessment is the process of identifying and defining geographic areas, groups of chemicals and exposure scenarios that are evaluated for further analysis. These decisions about the conduct of the assessment expand further to take into account appropriate groupings of chemicals using exposure information (Chapter 3) and judgments regarding similarity of toxic effects and the potential for interactions, the basis for toxicity groupings (Chapter 4). In the Risk Characterization the analyst may address broader elements such as appropriateness of the selected analytic scope, choice of chemicals for analysis, choice of exposure scenarios, criteria for grouping chemicals, identification of appropriate populations for analysis and an evaluation that seeks to determine if there are other important factors not being addressed in the analysis (i.e., looking at the analysis from "outside the box" to see if the analytic approach really makes sense). At the end of this process, the analyst identifies the types of effects that might occur, quantifies their likelihood in different populations and quantifies, where possible, the uncertainties in these estimates. The risks of any health outcomes that cannot be quantified are to be described qualitatively, along with suggestions regarding the kinds of information required for quantitative characterization of the likelihood that such a health effect could occur. The principles and guidance offered on these matters in the *Policy for Risk Characterization* (U.S. EPA, 1995b; see also U.S. EPA, 2000f) and *Science and Judgment in Risk Assessment* (NRC, 1994) are applicable to characterizing cumulative risks.

5.3. A RISK CHARACTERIZATION PROCESS FOR CUMULATIVE RISK ASSESSMENT

Figure 5-1 presents an approach for characterizing cumulative risks. Subsequent sections discuss each step in the process.

5.3.1. Populations. In the Problem Formulation phase and the analyses of exposure (Chapter 3) and toxicity (Chapter 4), the analyst identifies the relevant populations to be considered in the cumulative assessment. These can include the general population and vulnerable populations. In the general population assessment, it may be important to determine whether the exposure assessment accurately depicts exposure factor variability as well as typical and unique exposure pathways. Following are some

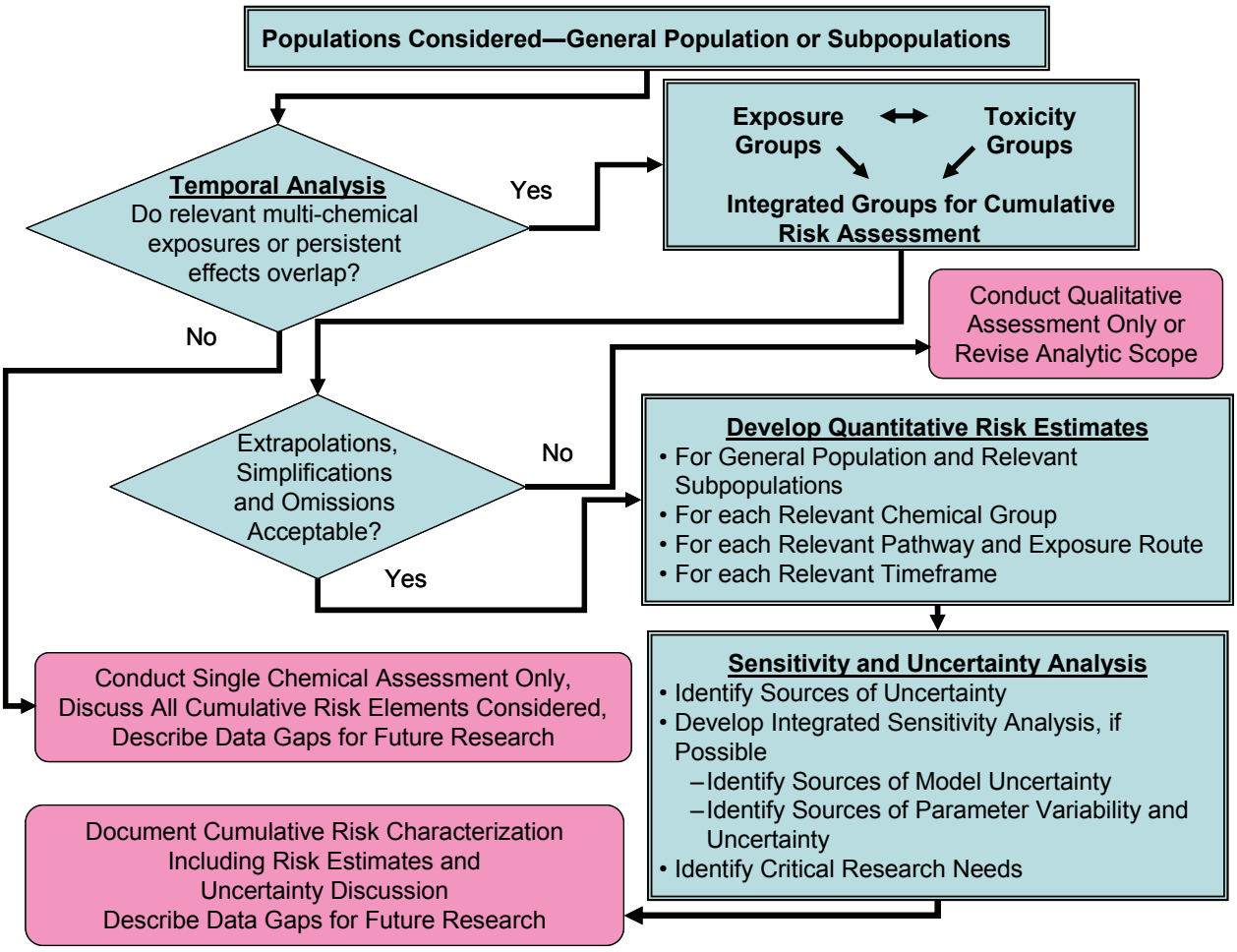


FIGURE 5-1
Schematic of Cumulative Risk Characterization Approach in this Report

example vulnerable populations that have been identified in cumulative risk scenarios and published in the literature:

- Fetuses – Spontaneous abortions from (possibly) short-term, multiple route maternal exposures to low doses of multiple drinking water DBPs (Waller et al., 1998)
- Rural resident – Neurological effects from chronic multiple route exposures to organophosphorous pesticides used in agriculture (U.S. EPA, 2002a)
- Subsistence fishing family – Cancer in adults exposed chronically via ingestion of fish containing PCBs (U.S. EPA, 1996b); neurotoxicities in children exposed *in utero* to methylmercury *via* fish consumption (U.S. EPA, 1997e; U.S. EPA, 2001b)
- Elderly – a potential combination of high exposure and high vulnerability in a susceptible population that may be 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)

The vulnerable subpopulations can be identified in the initial Planning and Scoping stage of the Problem Formulation phase of the assessment, during the exposure assessment, the dose-response assessment or Risk Characterization phase.

5.3.2. Temporal Analysis. For each subpopulation and the general population (if relevant), the analyst may determine whether there are multi-chemical exposures that occur over a toxicologically relevant timeframe(s), considering both TKs and TDs (Chapter 3). If no relevant overlaps are evident, then only single chemical assessment(s) are conducted. If there are relevant overlaps, resulting in exposure groups, then those groups are evaluated for toxicological similarity (Section 5.3.3).

The temporal relationships among exposures to different chemicals are a critical consideration in the estimation of cumulative risk. The initial analysis may involve an examination of the environmental fate of various contaminants over time (Chapter 3). Using this information for the various exposure media, the exposure analyst can estimate from the exposure assessment the temporal relationships of each compound to the other compounds. The exposure and toxicity analysts may then work together to consider the longevity of each chemical in target organs or tissues and how the dynamics and kinetics of each compound might influence the mode or mechanism and/or dose at a target site.

Some chemicals may bioaccumulate and persist in the blood or in target tissues for months or even years following exposure (e.g., methylmercury, cadmium). In contrast, many other environmental pollutants such as PCBs undergo significant redistribution to non-target tissues such as adipose, effectively decreasing the duration of exposure at a potential target site (Öberg et al., 2002). As such, characterizing the "effective" duration of a compound (i.e., time spent above a toxic threshold) in a target tissue and the manner in which a compound exerts biological effect (toxic mode of action, MOA) is critical.

The expression of mutagenic/genotoxic effects is presumably independent of the time-course of tissue exposure. That is, replication of errors in genetic material may persist long after the toxicant and its original (e.g., a DNA adduct) insult have been removed from the target tissue (U.S. EPA, 1991b, 2001f; IPCS, 1998). For most other modes or mechanisms of toxicity, the duration and magnitude (severity) of an adverse effect may be highly influenced by the dynamics and kinetics of compounds co-located within the same compartment (e.g., subcellular organelles, cells, whole organs or tissues). For example, exposure to an inducer of metabolic enzyme systems (e.g., cytochrome P450 family) such as chronic ethanol may increase the metabolism and clearance of environmental pollutants via upregulation of CYP2E1 expression/activity (Johns et al., 2006). Conversely, exposure to TCDD has been shown to enhance the accumulation of Cd, and likewise Cd inhibits the biotransformation of TCDD, thus influencing the bioaccumulation and potential toxicity within target tissues (Regoli et al., 2005). Thus, important factors in the estimation of cumulative risk involve characterization of the biological longevity of bioaccumulated compounds at a target site, the biological longevity of effects, the duration spent above a toxic threshold and mode or mechanism of action of each. Additionally, the restorative or regenerative capacity of the tissue(s) affected must be taken into account (e.g., liver versus brain).

5.3.3. Integrative Cumulative Risk Assessment. Based on the temporal analysis of the exposure and the toxicity information, the analyst forms final chemical groupings for use in the integrative cumulative Risk Characterization. This step consolidates the multichemical exposure data and the mixtures dose-response information. The integrated data might include extrapolations for dose-response elements (animal species, exposure route or duration, joint toxicity, population susceptibility) and conversions of measurement units (exposure or dose, toxic effects and assumptions regarding biological level of organization). Other simplifications (e.g., grouping chemicals by target organ instead of by more sophisticated knowledge of toxic MOA)

and other notable omissions (e.g., exclusion of certain exposure pathways, chemicals, subpopulations, toxic effects, toxicity pathways) may be identified.

For important decisions, expert elicitation may be used to develop final chemical groups. This practice relies on expert consideration of scientific theories and available data. The experts then provide judgments in the form of subjective probability distributions. These judgments can be combined and integrated into the analysis (DeGroot, 1970; Cooke, 1991); Evans et al. (1994) use this approach for estimating chemical carcinogenicity in the low-dose region of the dose-response slope.

5.3.4. Evaluation of Extrapolations, Simplifications and Omissions. In this step the analysts as a group (or an independent group) determines if the extrapolations, simplifications and omissions employed in the previous step are acceptable. Many of the extrapolations, simplifications and omissions will result from a lack of knowledge (e.g., lack of knowledge regarding the toxic MOA; uncertainty regarding exposure duration), which is sometimes referred to as epistemic uncertainty. The analyst will use scientific judgment regarding the grouping decisions (e.g., deciding that lack of a complete exposure pathway would eliminate a certain group of chemicals from the analysis) and agreements reached during Planning and Scoping (e.g., an agreement to retain certain relevant chemicals in an assessment regardless of their exposure levels). It is important to clearly and transparently describe the bases for these judgments, including the evidence available to support the judgment and the degree of consensus within the scientific community, so that the underlying logic can be evaluated further. If the extrapolations, simplifications and omissions are judged to be acceptable, then quantitative risk estimates are developed. If not, then the analyst describes the assessment qualitatively, highlighting the limitations in the data; alternatively, the analytic scope can be revised. In either case the limitations or needed data are described.

5.3.5. Develop Quantitative Risk Estimates. The analyst next develops quantitative risk estimates for each subpopulation and the general population (if relevant). This integrative step in the Risk Characterization includes each relevant chemical group, each relevant exposure pathway and route and all timeframes analyzed. Detailed methods are provided in Chapter 4.

5.3.6. Sensitivity and Uncertainty Analysis. Characterization of variability and uncertainty is integral to all risk assessment steps (Morgan and Henrion, 1990; NRC,

1994; Cullen and Frey, 1999). Variability refers to population heterogeneity, such as body weights that vary across individuals. Uncertainty is described as a lack of knowledge about the correct value for a specific parameter or the correct model. Both Chapters 3 and 4 discuss uncertainty in the context of exposure assessment and dose-response assessment, respectively.

In the sensitivity and uncertainty analysis for the Risk Characterization, the analyst identifies sources of uncertainty in the previous analytic steps and systematically evaluates their impacts on the final analytic results. This may include in-depth analyses of the uncertainties in the models and monitoring data used. If models are used extensively, the analysis could include an examination of model uncertainty (Cullen and Frey, 1999). Parameter uncertainty and variability are also evaluated at this stage of the analysis. Section 4 of this chapter provides additional detail on variability and uncertainty with respect to cumulative exposure assessment and cumulative dose-response assessment.

5.3.7. Cumulative Risk Characterization. Finally, the analyst develops the cumulative Risk Characterization for the integrative analysis. This includes a technical communication of the risk estimates, uncertainty analysis and critical data gaps. Risk estimates include a description of the expected toxicity for each population of concern, a quantitative estimate of the risk, and the size of the population likely to be affected. The Risk Characterization for that population is then a key result of the risk assessment and, at a minimum, includes the description of risk for the average population exposure, along with the size of the population. These population groups may 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 toxicological interactions. Such sensitivity might be related to physiologic characteristics or exposure (e.g., lifestyle) factors that could enhance the synergistic activity of the chemicals. This latter group is unique to cumulative risk assessment. The risks address those identified in the Problem Formulation phase and the toxicity groups via all major exposure pathways. 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 analyst could 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 describes 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 associated with 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 is 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). A correlation analysis between intake rates and body weights also may be needed to clarify the relationship between the two parameters.

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 risk assessments, 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) 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 includes 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, it is useful to include any information on the persistence or reversibility of the most likely effects.

Specific population subgroups of main concern might be identified in the Planning and Scoping stage of the assessment. Some subgroups might be linked to the initiating factor that led to the cumulative risk assessment. Other subgroups of concern might be identified during the exposure assessment or the dose-response analysis. 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 Planning and Scoping stage are included in the Risk Characterization. It is important that results are described in terms of the factors decided on during Problem Formulation to ensure that the questions of central concern to the stakeholders have been answered.

Several potentially sensitive population subgroups might be identified during the exposure and toxicity assessment steps. It is good practice to describe the risks to these subgroups 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 might need to be designed to avoid increasing exposures to potentially sensitive subgroups that might reside downwind of the air stripper.

5.4. VARIABILITY AND UNCERTAINTY IN EXPOSURE AND DOSE-RESPONSE

This section describes possible sources of variability and uncertainty in cumulative risk analyses, followed by discussions of variability and uncertainty with respect to cumulative exposure assessment and cumulative dose-response assessment.

5.4.1. Usefulness of Variability and Uncertainty Analyses in Cumulative Risk Assessments.

Understanding the uncertainty inherent in a cumulative risk assessment helps risk managers to understand the possible range of risks posed by the situation they are evaluating and provides additional insights into risk management opportunities at the site. Ultimately, uncertainty analyses help the risk manager avoid poor decisions and improve his or her appreciation for the potential ramifications of each alternative considered. While no single approach can be used to address all possible sources of variability and uncertainty in risk assessment, sensitivity analyses provide an opportunity to evaluate the confidence that can be placed in an assessment and to identify and prioritize critical research to improve future risk assessments. The NRC (1994) encourages the development of uncertainty analyses in risk assessments. The qualitative identification of sources of uncertainty and variability is currently a routine

component of most human health risk analyses, regardless of their level of sophistication (e.g., screening level analyses include an identification of sources of uncertainty and variability).

The EPA recognizes that secondary data are data used for a purpose other than that for which they were collected. That does not imply that their quality is reduced but that the appropriateness of their inclusion in the given application be justified.

The quality of experimental data used in a cumulative Risk Analysis can differ widely and needs to be addressed in a cumulative risk assessment. The data quality issue is particularly important when the qualitative measures (e.g., response levels or chemical measurement data collected at the site) or critical qualitative findings (e.g., criticality of a certain biochemical event in an MOA pathway or assumptions regarding the environmental fate of mixture components released to the environment) are introduced into the cumulative risk assessment.

5.4.2. Exposure Assessment Uncertainty and Variability.

5.4.2.1. Variability in Cumulative Risk Exposure Assessments—Variability refers to population heterogeneity, such as tap water consumption rates varying across individuals and over time (e.g., the same individual may consume more water during hot arid weather than cold weather leading to seasonal exposure variations). Studies exhibiting increasing sophistication have been undertaken to increase the understanding of variability in exposure factors (e.g., drinking water intake rates) in key subpopulations (e.g., women of reproductive age, pregnant women and children) (U.S. EPA, 1997c). While tap water consumption can be measured accurately, the true values will vary across the population and no increase in the level of precision in measurement techniques will reduce this variability across the population. A second component of variability involves analyzing correlations among variables (e.g., correlations of food intake rates and body weights). Correlation analyses among exposure factors also continue to improve.

5.4.2.2. Uncertainty in Cumulative Exposure Assessments—Uncertainty or, more specifically, epistemic uncertainty, is described as a lack of knowledge about a specific exposure pathway, measure or estimate. Uncertainty is typically more difficult to quantify than variability.

The exposure scenarios developed for a cumulative risk assessment involve multiple chemicals and multiple environmental media. In this approach, analyses of individuals who are co-exposed to chemicals may rely on dynamic fate models. The

uncertainties in these models and their implications on the assessment results may be discussed in the Risk Characterization.

The concentrations of these chemicals in various environmental media may be estimated through direct analytical measurement, predictive modeling or some combination of the two. Thus, it may be important to examine the sensitivity and specificity of different analyses used to measure the concentrations of different chemicals or the same chemicals in different media and, if possible, integrate that information into the risk assessment or the sensitivity analysis. The quantitative uncertainty of model predictions for concentrations of chemicals in different media may also vary. While the scientific understanding of some environmental fate processes may be well measured and understood, others may be less so. Mathematical models describing well understood processes may be accepted generally by the scientific community. For poorly understood processes, there may be competing models. In such situations, it may be important to analyze model uncertainties.

Exposure assessment uncertainties also include sources of error such as inaccuracies in the analytical methods for quantifying the level of chemicals in environmental media (e.g., surface water). There is a true value for such a concentration in this example, but the available methods may not be sensitive enough to provide an accurate answer. In the exposure assessment, good scientific practice would dictate that the treatment of data determined to be below the analytic detection limit be carefully considered because assumptions regarding the “true” contaminant concentrations in such samples influence exposure estimates (e.g., Fristachi and Rice, 2007). When combining information on chemical concentrations in the characterization, clear identification of the limits of the techniques used to estimate these concentrations is necessary. If the authors of such reports present error bounds, then it is good practice to state the types of factors included and not included in the analysis.

Ingestion, inhalation and dermal contact rate information may be developed from different sources. The quality of the sources could vary. The EPA *Exposure Factors Handbook* (U.S. EPA, 1997c) recommends specific ingestion rates for foods such as vegetables and freshwater fish and drinking water; it describes many of the limitations in the underlying studies. The relevance of the data from the recommended studies to the populations being evaluated also may be examined. For example, freshwater fish consumption rates among individuals in certain Native American tribal groups may be greater than those for the general U.S. population (e.g., Peterson et al., 1995; Toy et al., 1995); these populations also may consume parts of the fish that are typically not consumed by the general population.

In a traditional risk assessment, an exposure 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 exposures then might encompass a number of events at several locations over broad and varied time periods. 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.

Finally, 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 (e.g., 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 identifies 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.

5.4.2.3. Methods for Uncertainty Analysis—Methods to quantify uncertainty are better developed for the field of exposure assessment than the fields of hazard identification, dose-response assessment and Risk Characterization. Most exposure assessments quantitatively estimate variability and uncertainty using probabilistic techniques that make use of Monte Carlo simulations and there is EPA's *Guiding Principles for Monte Carlo Analysis* (U.S. EPA, 1997f). Probabilistic exposure models allow for a robust examination of the factors that lead to exposures and provide a basis for addressing highly exposed populations. These types of models can examine and evaluate the impacts of parameter uncertainty and variability. Intake rates and body weights are highly variable in the population so using a single-point estimate for these variables instead of probability distributions ignores inherent variability that may influence exposure estimates. Monte Carlo methods lead to an approximation of a sampling distribution by statistically incorporating probability distributions of concentrations in media to which people are exposed and exposure factors, such as those found in the EPA *Exposure Factors Handbook* (EFH) (U.S. EPA, 1997c). The EFH provides a summary of the available statistical data on various factors used in assessing human exposure. The factors provided include drinking water consumption;

soil ingestion; inhalation rates; dermal contact factors including skin area and soil adherence; consumption of fruits and vegetables, fish, meats, dairy products and homegrown foods; breast milk intake; human activity factors; consumer product use; and residential characteristics.

Monte Carlo analysis is very useful because it leads to an approximation of an estimate of the statistic's sampling distribution by treating observed data as if it were the unknown population and then sampling from this new population. Within a Monte Carlo simulation, values from each distribution are randomly selected and input to the model; the output of each iteration is stored in a new distribution that is subsequently analyzed (U.S. EPA, 1997f).

Because the output of the simulation provides a distribution of results, central tendency estimates of exposure to the chemicals comprising the mixture as well as the statistical dispersion around the central tendency estimate (e.g., 5^{th} and 95^{th} percentile values) can be evaluated. Although beyond the focus of the discussion in this chapter, other techniques, such as 2-dimmensional Monte Carlo methods, attempt to quantitatively distinguish between sources of variability and uncertainty (Morgan and Henrion, 1990; Hoffman and Hammonds, 1994; Simon, 1999). Other methods that do not randomly sample from the statistical distributions can also be employed, depending on the goals of the analysis, such as Latin Hypercube sampling, which disproportionately draws samples from the upper and lower tails of the statistical distribution (Cullen and Frey, 1999).

5.4.3. Uncertainty and Variability in Dose-Response Assessment for Cumulative Risk Assessment. Although a variety of quantitative uncertainty methods have been developed and extensively utilized in exposure assessment, the state of this practice in dose-response analysis is not as advanced. Most analyses of uncertainty and variability in dose-response assessment have focused on the qualitative identification of the sources of uncertainty (e.g., extrapolation from rodent bioassay data to human dose-response estimates) or the application of default uncertainty factors. Thus, uncertainty and variability analyses in cumulative risk assessment ultimately may require both the development of new methodological approaches and also consideration of additional variables beyond those considered in single chemical dose-response analysis.

5.4.3.1. Hierarchy of Data Sources for Assessing Exposure-response Relationships for Chemical Mixtures—When evaluating sources of dose-response

data for chemical mixtures, EPA's mixture guidance documents (U.S. EPA, 1986a, 2000a) suggest the following order of preference for data:

1) The mixture of interest
2) A sufficiently similar mixture
3) Mixture components

Dose-response data from human studies is preferred to animal bioassay data; animal toxicology data is preferred to *ex vivo*, *in vitro* and *in silica* data.

Often, epidemiology data (i.e., occupational data) and toxicological data are available only for commercial mixtures of environmental contaminants. If the environmental mixture is similar to the commercial mixture, then the commercial mixture dose-response data can be utilized in the assessment. If, in the environment, the mixture components are differentially transported, partitioned, transformed, degraded or bioaccumulated, then the use of the commercial mixture dose-response data can be highly uncertain, because the environmental mixture to which people may be exposed is likely to differ from the commercial mixture. Consequently, the toxicity of the toxicologically tested mixture may differ from the environmental mixture and such data may not be very useful in the dose-response analysis. The analyst may judge whether the environmental mixture is sufficiently similar to the tested; these analyses are typically based on ratios and concentrations of components. If the analyst judges the mixtures to be sufficiently similar then the dose-response data from the tested mixture is used. If the mixtures are judged to not be sufficiently similar, then mixture component data are used (Chapter 4; see also U.S. EPA, 1986a, 2000a).

Epidemiologic data is preferred over animal toxicological data, because, following exposure, there may be differences in absorption, distribution, metabolism (retention) and elimination across species. Also, the toxicity (toxicodynamics) of mixtures can vary across species. Even if there are epidemiologic data, there are possible sources of uncertainty to consider when using epidemiologic data for cumulative risk. These include (1) study design issues such as potential confounding and other biases, inadequate sample size and follow-up, (2) the choice of the dataset, (3) specification of the dose-response model, (4) estimation of exposure and dose and (5) unrecognized variability in susceptibility (Stayner et al., 1999). Further, it is important to note that exposures to the same environmental mixtures can vary substantially across time and place due to differential partitioning, etc. (see previous discussion of environmental fate and transport factors and sufficient similarity; also see discussion of sufficient similarity in U.S. EPA, 2000a).

In vivo whole mixture data (e.g., the testing of concentrated whole DBP mixtures in rodent bioassays conducted by Simmons et al. [2002]) are preferred over *ex vivo*, *in vitro*, and *in silica* data. *In vivo* data account for absorption, distribution, metabolism and elimination of the mixture. The other listed sources of toxicity data either do not account for these factors or only partially account for them (e.g., addition of the S9 fraction to *Salmonella* reverse mutation assays). These other sources of toxicity data may not be useful for identifying secondary effects of chemical mixtures (i.e., effects associated with doses that are higher than those needed to elicit the primary or critical effect).

The uncertainties associated with simple mixture component methods such as the HI, RPFs and response addition are generally considered to be larger than those associated with dose-response data based on whole mixtures. For example, analyses that rely on such methods may not assess the toxicity associated with all components of the mixture.

The HI approaches are based on a defined RfD or a surrogate for secondary effects (see Text Box 4-2 on Target Organ Toxicity Doses in Chapter 4). The RfD is derived by the application of uncertainty factors, which may each be thought of as values from a distribution of values (when the true value is unknown) ranging from 1-10 (Swartout et al., 1998).[2] In addition, the true value of the NOAEL or LOAEL is subject to the details of experimental design of the toxicity study, not the least of which is the selection of dose spacing. Thus, it is important to recognize the uncertainty in the UFs themselves and in the resulting RfDs. Additional attention may be given to whether the critical effect was determined in animals or was detected in humans—RfD values resulting from the latter case are more certain than RfD values derived from toxicity characterized in research animals.

Additivity methods such as dose addition and response addition (U.S. EPA, 2000a) are relatively simple mathematical models depicting responses to mixtures comprised of chemicals sharing a common toxic MOA or independent MOA while affecting the same target tissue or toxic endpoint, respectively. These component models typically are associated with greater uncertainty than dose-response assessments developed when the toxicity of the whole mixture is evaluated.

It may be important to discuss the uncertainties associated with grouping mixture components into common MOA subgroups or in assuming that they independently affect the same target tissue and to describe the implications of other toxicity groupings.

[2] The EPA has recognized the potential overlap in the areas of uncertainty by establishing a cap of 3000 when four areas of uncertainty are required to derive a reference value (U.S. EPA, 2002e).

When determining groups of chemicals (as shown in Figure 4-7b), the evaluation of component data includes steps that require consideration of target organ-specific data. Toxicity databases, such as the EPA IRIS database, may provide toxicological information only on a single critical effect (i.e., that effect occurring at the lowest exposure level). Additional data such as those in other EPA documents, ATSDR toxicological profiles and interaction profiles, or those obtained from primary literature searches may be necessary to identify additional effects and target organs. Whether adequate dose-response data are available affects the grouping of chemicals and the potential for estimating the joint toxicity of the chemical combinations. When information on secondary effects is inadequate, it may be important to address the impact of this uncertainty, particularly regarding joint toxicity that may be underestimated for those secondary effects.

Many biological systems comprise diverse biochemical processes and multiple organs or tissues. A single chemical insult to a specific part of the overall pathway (e.g., endocrine function) may result in a toxicity seemingly unrelated to the chemico-biological interaction. Multiple chemicals may have different mechanisms of action yet impact the same system. These may result in upregulation or downregualtion of individual steps of the system. The end result is that some effects may compensate for other effects and that some effects may interact in a synergistic or additive manner. If there are credible data that support synergistic or antagonistic interactions, then these may be included in the cumulative risk assessment. However, in the absence of such data, the assumption of a common or independent MOA used to support the choice of dose addition or response addition, respectively, is identified as an area of assumption and uncertainty.

5.4.3.2. Choice of Dose Metric—Chemical components of a mixture may contain parent compounds and environmental transformation and degradation products. Thus, chemical metabolism and its effect on toxicity may be important to consider. When toxicity arises due to the formation of a bioactive metabolite, exposures to the metabolite are better justified as dose metrics than exposure to the parent chemical. To the extent possible, cumulative risk assessments identify when toxicity is due to a chemical metabolite.

Mixtures dose response data also may be based on internal dose measures (e.g., measures of chemicals in blood or in the target tissue). Such measures may address chemical absorption, distribution, metabolism and elimination. Such measures may be preferred to potential dose measures. When toxicity results from the formation

of a metabolite, internal dose measures of the metabolite are better justified as dose metrics than potential doses of the parent chemical.

5.4.3.3. Analysis of Uncertainties Associated with Dose-response Data— Both model-independent and model-dependent approaches using toxicological and/or epidemiologic data are used in risk assessments. Major issues with choosing and implementing different approaches to dose-response estimation include knowledge of MOA and biological relationships at low dose. Due to limitations in experimental or epidemiologic data, dose-response relationships are often extrapolated to the low dose region from measured responses at high doses. Exposure misclassification can also distort dose-response relationships in epidemiological studies, in particular for low doses or exposures. Therefore, toxicological data may be preferred for dose-response assessments for certain exposures. Although common practice in risk assessment, extrapolation from the observed region of the dose-response curve to low dose levels introduces uncertainty into the assessment.

Most dose-response models output central tendency estimates and confidence limits based on variability from the dose-response function, but they provide little or no characterization of uncertainty. Uncertainty can be introduced into a dose-response estimate and subsequent risk values through model structure and parameter selection.

Uncertainties in quantitative data are, perhaps, the most worrisome in that the cumulative risk assessment may be based on a less than certain measure of effect or exposure (in the context that HQs are defined as exposures divided by acceptable level of exposures). Both concerns over data quality and uncertainty in quantitative data may be based on several factors including proximity of the measured event to the toxicological event of interest, the likelihood of measurement (detection) error, erroneous selection of a given dose-response model, biases (reported or not) in experimental design as well as incongruence between the study purpose and the risk assessment application. These technical potential defects and uncertainties can adversely impact confidence in the cumulative risk assessment outcome through imparting a higher level of uncertainty in quantitative data, owing to data quality issues including issues of data collection and data application. These issues may be highlighted when combining data from multiple single-chemical studies to develop a cumulative risk assessment.

Commonly, uncertainty in toxicological data is addressed using *uncertainty factors*. Uncertainty factors are used to compensate for deficits in knowledge concerning the accuracy of toxicity data and the difficulty in estimating the health effects

in a different species and/or in different exposure conditions. Other methods, such as PBPK modeling using Monte Carlo simulation are available for evaluating human variability in the dose-response assessment.

5.4.3.4. Consideration of Multiple Effects—Cumulative risk assessments also address multiple effects that result from exposures to one or more chemicals. Multiple effects of a chemical mixture include the primary (critical effect) and secondary effects (effects that result from higher exposures than the exposures producing primary effect. Because the critical organ is already affected, further changes or alterations in the toxicity in that organ are seldom studied or documented. Secondary effects may arise due to several reasons:

- The metabolism of the compound could become saturated with increasing dose and higher doses may result in circulating levels of toxic parent chemical or higher circulating levels of a toxic metabolite that may saturate clearance mechanisms
- Damage to the primary organ
- A higher degree of resistance or repair capacity in the secondary organs such that a higher level of exposure is required to produce these effects
- Secondary tissues may differ in the inherent biochemistry and cellular organization from the primary organ such that a different MOA is active in the secondary tissues, and the exposure concentrations necessary to drive that MOA are higher than the exposure necessary to stimulate the MOA in the primary organ

In general, the latter is the assumed reason for secondary effects in cumulative risk assessment, but the former three circumstances may be considered. These differ from the latter in that the latter may be more directly employed as the basis for the assumption of independence between the critical effect and secondary effects.

5.4.3.5. Duration of Effects—In developing a cumulative risk assessment, it is assumed that the period during which effects will become manifest is similar for all contaminants. Data may be available to address whether certain chemicals differ in their periods of latency for observable health effects. When different latency periods (and durations of toxic effects) exist for components of a chemical mixture, then the likelihood of a simultaneously-expressed toxicity is reduced. When possible, it may be useful to address the quantification of the latency period and duration of toxic effects and uncertainty in these estimates.

5.4.4. Variability and Uncertainty Summary. In summary, quantifying the sources of variability and uncertainty in the integrative analysis can be quite complicated. The types of issues typically evaluated in quantitative uncertainty analyses include model uncertainty, parameter uncertainty and uncertainty in assumptions that are developed because of missing information. Identification of the sources of uncertainty in an exposure assessment can increase the level of confidence in results and may further help to determine the type of research needed to reduce it in future assessments. Addressing uncertainty and variability increases the clarity and transparency of cumulative risk assessments and may be quantitatively estimated to the extent possible. When only qualitative characterizations are provided, their basis is described along with suggestions for ways to improve and quantify those characterizations.

As has been discussed in several previous 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 a CHI<1, the indication of safety may be false due to an information gap. The CHI calculation may be evaluated and quantified where possible to estimate 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 are placed in a watch list, so that when sufficient information becomes available, their contribution to the cumulative risk can be assessed.

5.5. 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. The goal of this information sharing is to develop accurate estimates of risks. Because cumulative risk assessment includes many factors, some of which vary over time, the ideal risk calculations would utilize supporting measurements and studies that may not exist. For example, Section 4.7.1 presents a modified RPF approach for exposure to mixtures by multiple pathways. The RPF approach requires information demonstrating that the chemicals included in the calculation have similar toxicological MOAs. Such information is not always available on all chemicals of concern. To illustrate the Risk Characterization issues involved with quantitative risk assessment, some, but not all, of the quantitative approaches presented in Chapter 4 are examined here in terms of feasibility and impact on the risk assessment.

5.5.1. 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 CHI. The common dose-additive HI combines multi-chemical exposures by summing the component exposure levels after each has been scaled by division by that chemical's RfD (for ingestion) or RfC (for inhalation). (See Section 4.2.2.1 for a complete description of the dose-additive HI.) The CHI as discussed here expands on the uses and interpretation of the CHI used by Superfund in site evaluations. 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 HQ in the usual way. EPA's Risk Assessment Guidance for Superfund (1989a) instructs analysts 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 that 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.

5.5.1.1. 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*:

$$HQ_{jk} = E_{jk} \Big/ RV_{jk} \tag{5-1}$$

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:

$$HQ_j = \sum_{k=1}^{m} HQ_{jk} \tag{5-2}$$

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

$$CHI = \sum_{j=1}^{n} HQ_j \tag{5-3}$$

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 = 0.

5.5.1.2. 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 is not 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 or indicate 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 and nature of the CHI is generally examined. The analyst may re-evaluate the exposure assessment to determine if more details are available, such as information suggesting co-exposure by multiple pathways and review the dose-response assessment, particularly the assumptions of similarity and no interaction (see Section 5.2.1.3), along with the other assumptions described in the EPA mixture guidance (U.S. EPA, 2000a). The interpretation of CHI is not different from that of any HI calculation. CHI is a risk indicator. If CHI>1, then the analyst examines the individual HQs in the calculation to see if any one chemical, one exposure route or small group of chemicals is driving the risk indicator.

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 analyst evaluates the pathways involving those interacting chemicals 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).

Because the CHI involves simple sums, the summation can proceed in either order:

- Either sum across pathways for each chemical and then across chemicals (Superfund's approach, given above in Equations 5-2 and 5-3)
- Sum across chemicals to get a pathway specific HI and then sum HI’s 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. This 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 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 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 an identified mechanism of toxicity at a dose significantly lower than the dose 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).

5.5.1.3. Assumptions with Cumulative Hazard Index—The Risk Characterization step addresses 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 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

- There are no interactions across chemicals in terms of fate and transport or in terms of single or multi-route 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 assumptions for the CHI are

- each of the chemicals incorporated into the CHI are toxicologically similar for all the pathways included in its pathway HQ calculation and have no significant portal of entry effects (route-specific primary toxicity). Similarity here can be indicated by the same toxic MOA, same primary target organs or similar general type of toxic effect (e.g., cancer, reproductive toxicity). (For further discussion of toxic similarity, see Section 4.4.) 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 are 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; and
- perhaps most unique to cumulative risk assessment, the chemicals do not affect each other's fate and transport, regardless of pathway.

Text Box 5-3 shows an example illustration. Text Box 5-3b briefly illustrates calculations using dose and response addition.

Example—Site Safety *(Text Box 5-3)*

Consider the case where a cumulative risk assessment goal is to determine with high confidence whether a site is safe prior to initiating any site clean-up activities. One risk description could include an overly conservative (health protective) estimate, perhaps based on the high-end exposure estimates for each of the possible routes. If the risks predicted by this conservative approach are considered by the risk manager of the site to be within acceptable levels, then any refined 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 an HI 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, 2001c). If CHI>1, then additional evaluation, perhaps a more refined analysis, is recommended. Because the CHI is a conservative overestimate of the HI, a value exceeding the acceptable levels does not imply the expectation of toxic effects but only that a more detailed risk assessment is needed. For screening analyses, conservative CHI criteria that are <1 also can be employed by the risk manager.

5.5.2. Categorical Regression Calculations for Multiple Effects and Pathways.

One complication of cumulative risk, recognized in the EPA'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 subdivide the Risk Characterization so that each division of the document addresses only one of the likely toxic effects. This approach provides the opportunity to include details that may be difficult to incorporate into a single comprehensive risk characterization. An alternative is to address the multiple effects directly in a single composite measure as described in Chapter 4.

5.5.2.1. Calculations—Two formulas are given in Chapter 4 for describing multiple effects for k = 1,...,n chemicals (see Section 4.5.1). These are restated here, one based on the HI (Equation 5-4) and one based on response addition (Equation 5-5):

$$HI(effects) = \sum_{k=1}^{n} \left(\frac{E_k}{BMDL_k / UF_k} \right) \tag{5-4}$$

and

$$R_m(effects) = \sum_{k=1}^{n} P_k(severity > 2) \tag{5-5}$$

or more accurately as

$$R_m(effects) = 1 - \prod_{k=1}^{n} P_k(severity \leq 2) \tag{5-6}$$

where:

BMDL = Benchmark dose lower bound

UF = Uncertainty factor.

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. (Greater detail about these concepts can be found in Chapter 4 and in Appendix C.)

Equation 5-6, R_m(effects), is the probabilistic risk of any adverse effect for the mixture. It 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 (e.g., P_k<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.

Equation 5-4, HI(effects), represents the HI for multiple effects from exposure to the mixture. 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 assumption of 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. The interpretation of the risk addition approach is straightforward 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.

For both evaluations of multiple effects, R_m(effects) and HI(effects), the effects observed in the animal studies are converted to severity categories, and then the model produces the probability of observing a certain severity of effect, given dose. When applied to a cumulative risk problem, the result does not correlate to any particular health effect in the population but only provides evidence of whether or not there are mixture risks of concern, taking into account that the chemicals cause multiple health effects. If these metrics are large enough to raise concerns for a certain exposure

scenario, then additional investigations may evaluate the population for health impacts, or a decision could be made to begin some type of remediation.

5.5.3. Assumptions with Multi-route Formulas for Multiple Effects. The calculation formulas for hazard or risk, for multiple effects by multiple routes, are similar to those used 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 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.

5.5.4. Combination of Exposures of Different Time Frames. Risk estimates for different time frames are developed by the analyst for 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 (e.g., 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 may be inappropriate measures of toxicity (Boyes et al., 2000). For longer exposure periods, simple cumulative dose (Haber's rule) often is inappropriate although a modified form does seem acceptable as a dose-duration metric. The combining of joint exposures over differing time frames uses the exposure metric appropriate to each exposure period.

The EPA and various scientists have published guidance, issue reports and research results on the impact of exposure duration on toxicity but, to date, these only consider 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 complications with cumulative risk assessment include (1) the potential overlap of exposures of different durations, (2) the persistence of an internal dose exhibited by a long half-life in the body (e.g., half-life of methyl mercury is estimated to be 45-70 days [U.S. EPA, 2007]) and (3) the persistence of an effect (e.g., the classical toxicodynamic concept of cancer initiation vs. cancer promotion). The combination exposures are evaluated jointly, as described in Chapters 3 and 4. When exposure duration is short, less than a few days, then the analyst may undertake the following steps:

- Estimating 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 or internal dose concentrations, yielding a higher exposure level for the short duration. The analyst may also estimate the persistence of the short-term physiologic changes at the cellular or tissue level (see Section 5.2.4 below).
- Developing a Risk Characterization specific to this short exposure period, focusing on those significant effects that do not persist beyond the short exposure period.
- Determining whether any impacts from the short exposure (e.g., changes in cell populations, upregulated enzymes) are likely to persist well into the longer exposure period. Those effects are 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.

Clearly, additional research on risks posed by exposures to multiple chemicals over different time frames would be useful.

5.6. OUTCOMES FROM CUMULATIVE RISK CHARACTERIZATION

The outcome of the cumulative Risk Characterization may provide a useful integration of the data needed by the risk manager to make decisions regarding a cumulative risk initiating factor. 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 are communicated clearly, with important issues and uncertainties highlighted. Finally, it may be useful to articulate the identification of data gaps, chemicals placed on a watch list and research needs that may improve the Risk Characterization.

5.6.1. Interpretation of Results in the Context of Interaction Factors. The Risk Characterization may 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 include a quantification of toxicological interactions using the Interaction-Based HI (Section 4.6.2) can show numerically how the remediation may have affected the risks by calculating this metric before and after remediation. Other summaries that may include only a qualitative indication of the direction of potential interactions might still be useful for setting priorities or changing the degree of conservatism used in the assessment. Table 5-1 illustrates whether joint toxicity is greater than, less than or equal to dose addition for oral exposures to binary combinations of Cd, Pb, As and Cr (ATSDR, 2004). This information can be used to qualitatively modify the interpretation of an additive (HI) calculation containing these chemicals.

Background exposures, those exposures that are not necessarily site-related or source-related, also can contribute to interactions. In many risk assessments, site contamination is often assessed as an incremental exposure, and thus incremental risk, i.e., the risk from the site exposure that exceeds background. Where possible, in cumulative risk assessments background exposures are included in the exposure estimate and in evaluations of interactions. Inclusion of background sources of exposure may improve the characterization of population risk. These also can facilitate comparisons of various sources of exposure (e.g., exposures from a group of sources vs. background) in the analysis.

TABLE 5-1

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

Metal Interactions	Blood	Kidney	Neurological	Male Reproductive	Skin	Cardiovascular
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		

*All exposures are oral. This table summarizes information in Table 4-2.
Source: ATSDR (2004).

5.6.2. Interpretation of Results in Context of Problem Formulation. Results highlight those risk estimates that address the issues identified in the Problem Formulation phase according to the consensus details of the Planning and Scoping phase (see the Planning and Scoping documents referred to in Chapter 1 for details.) The risk assessment may contribute useful information to the risk management decisions. In particular, the uncertainties may 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 Planning and Scoping stage and Problem Formulation phase may be revisited. For example, if the primary concern is risks caused by contamination at the site, then a comparison may be needed with risks from exposures to background or off-site contamination.

5.6.3. Interpretation of Results in Context of the Initiating Factor. Different initiating factors may require different approaches to the cumulative risk assessment and thus result in different outcomes and interpretations. For example, epidemiologic approaches may be the best choice when the initiating factor for a cumulative risk assessment is a population illness identified by a disease cluster (Section 2.5). When the initiating factor is a particular source, environmental concentration or biomonitoring result, the investigation may also require analyses using epidemiologic methods that can be linked with the examination of chemicals and their sources. Thus, results will be relevant to an existing population with known exposures to environmental chemicals and observable health conditions. The observable health conditions can then be linked with chemical exposures and the risks to subpopulations can be calculated (e.g., using relative risk measures such as odds ratios). Vulnerability factors (e.g., age, smoking, health status) are generally accounted for in epidemiologic analyses and can be discussed in the Risk Characterization.

The approaches on multiple route exposures to multiple chemicals, discussed in Chapters 3 and 4, may be used for any of the initiating factors. In certain cases, estimates of potential impacts on human health may be made for a hypothetical population (e.g., a population that may be exposed due to future land uses of a contaminated site). This could be done even when the initiating factor is a current population illness. Such analyses may include expected or anticipated exposures to environmental chemicals and the potential for effects that are not yet exhibited but may occur in later years (e.g., cancers that are expressed only after a long latency period).

Thus, a chemical- or source-based analysis may be necessary and a link between disease endpoints and chemical exposures articulated, along with an estimate of potential population risks. The analyst may perform a WOE assessment to support whether exposures to multiple chemicals are occurring and if significant health effects may be anticipated in the population of interest. The population characteristics may need to be articulated, including consideration of vulnerability factors.

5.7. SUMMARY

In summary, this chapter has stressed the importance of the Risk Characterization phase of cumulative risk assessment and has endeavored to consider issues in the context of evaluating multiple chemicals, exposures and effects, including interaction effects, with respect to the population characteristics. Issues regarding uncertainty, variability and sensitivity analysis have been discussed and a schematic (Figure 5-1) has been presented for conducting a cumulative Risk Characterization. An integrative technical analysis of the predicted risks is typically produced, as well as a summary of the results and uncertainties of the Risk Analysis. Risk Characterization results may be used by risk managers in the final Decision-Making stage of a cumulative risk assessment; thus the Planning and Scoping process, data sources, analytical techniques, logic used to make various technical decisions and uncertainty analysis must be scientifically sound and presented in a transparent manner.

6. REFERENCES

ACS (American Chemical Society). 2003. Long-Range Research Initiative. Available at http://www.uslri.org/.

Alavanja, M.C.R., D. Sandler, S. McMaster et al. 1996. The agricultural health study. Environ. Health Perspect. 104(4):362-369.

Alavanja, M.C.R., N.L. Sprince and E. Oliver. 2001. Nested case-control analysis of high pesticide exposure events from the Agricultural Health Study. Am. J. Ind. Med. 39(6):557-563.

Alavanja, M.C.R., C. Samanic, M. Dosemeci et al. 2003. Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study Cohort. Am. J. Epidemiol. 157(9):800-814.

Amdur, M.O., J. Doull and C.D. Klaassen. 1993. Casarett and Doull's Toxicology, 4th ed. McGraw-Hill, Inc., New York, NY.

ARB (Air Resources Board). 1997. Chlorine. Available at http://www.scorecard.org/chemical-profiles/html/chlorine.html. Also see NPI, 2005 (as cited in Scorecard, accessed 2006).

Arcos, J.C., Y.T. Woo and D.Y. Lai. 1988. Database on binary combination effects of chemical carcinogens. Environ. Carcinogen. Revs. J. Environ. Sci. Health (Part C). 6(1):1-164.

Aschengrau, A., S. Rogers and D. Ozonoff. 2003. Perchloroethylene-contaminated drinking water and the risk of breast cancer: additional results from Cape Cod, Massachusetts, USA. Environ. Health Perspect. 111(2):167-173.

ATSDR (Agency for Toxic Substances and Disease Registry). 1994a. Toxicological Profile for Chlordane. U.S. Department of Health and Human Services, Public Health Service. May. Available at http://www.atsdr.cdc.gov/toxprofiles/tp31.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 1994b. Toxicological Profile for 1,1-Dichloroethene. U.S. Department of Health and Human Services, Public Health Service. May. Available at http://www.atsdr.cdc.gov/toxprofiles/tp39.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 1996. Toxicological Profile for cis-, trans-1,2-Dichloroethene (update). U.S. Department of Health and Human Services, Public Health Service. August. Available at http://www.atsdr.cdc.gov/toxprofiles/tp87.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 1997a. Toxicological Profile for Chloroform (update). U.S. Department of Health and Human Services, Public Health Service. September. Available at http://www.atsdr.cdc.gov/toxprofiles/tp6.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 1997b. Toxicological Profile for Tetrachloroethylene (PERC). U.S. Department of Health and Human Services, Public Health Service. September. Available at http://www.atsdr.cdc.gov/toxprofiles/tp18.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 1997c. Toxicological Profile for Trichloroethylene (TCE). U.S. Department of Health and Human Services, Public Health Service. September. Available at http://www.atsdr.cdc.gov/toxprofiles/tp19.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 1997d. Toxicological Profile for Vinyl Chloride (update). U.S. Department of Health and Human Services, Public Health Service. September. Available at http://www.atsdr.cdc.gov/toxprofiles/tp20.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 1999a. Toxicological Profile for Lead. U.S. Department of Health and Human Services, Public Health Service. July. Available at http://www.atsdr.cdc.gov/toxprofiles/tp13.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 1999b. Toxicological Profile for Cadmium (Update). U.S. Department of Health and Human Services, Public Health Service. July. Available at http://www.atsdr.cdc.gov/toxprofiles/tp5.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 1999c. Toxicological Profile for Mercury. U.S. Department of Health and Human Services, Public Health Service. March. Available at http://www.atsdr.cdc.gov/toxprofiles/tp46.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 1999d. Toxicological Profile for Uranium. U.S. Department of Health and Human Services, Public Health Service. September. Available at http://www.atsdr.cdc.gov/toxprofiles/tp150.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 2000a. Toxicological Profile for Arsenic (Update). U.S. Department of Health and Human Services, Public Health Service. September. Available at http://www.atsdr.cdc.gov/toxprofiles/tp2.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 2000b. Toxicological Profile for Chromium (Update). U.S. Department of Health and Human Services, Public Health Service. September. Available at http://www.atsdr.cdc.gov/toxprofiles/tp7.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 2000c. Toxicological Profile for Polychlorinated Biphenyls (PCBs) (update). U.S. Department of Health and Human Services, Public Health Service. November. Available at http://www.atsdr.cdc.gov/toxprofiles/tp17.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 2000d. Case studies in environmental medicine: arsenic toxicity: exposure pathways. October. Available at http://www.atsdr.cdc.gov/HEC/CSEM/arsenic/exposure_pathways.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 2001. Toxicological Profile for 1,2-Dichloroethane. Update. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA. Available at http://www.atsdr.cdc.gov/toxprofiles/tp38.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 2002a. Toxicological Profile for Aldrin and Dieldrin. U.S. Department of Health and Human Services, Public Health Service. September. Available at http://www.atsdr.cdc.gov/toxprofiles/tp1.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 2002b. Toxicological Profile for Beryllium. U.S. Department of Health and Human Services, Public Health Service. September. Available at http://www.atsdr.cdc.gov/toxprofiles/tp4.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 2002c. Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA.

ATSDR (Agency for Toxic Substances and Disease Registry). 2003a. Draft Toxicological Profile for Carbon Tetrachloride. Agency for Toxic Substances and Disease Registry, Atlanta, GA. September. Available at http://www.atsdr.cdc.gov/toxprofiles/tp30.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 2003b. Draft Toxicological Profile for Nickel. U.S. Department of Health and Human Services, Public Health Service,. September. Available at http://www.atsdr.cdc.gov/toxprofiles/tp15.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 2003c. Draft Toxicological Profile for Zinc. U.S. Department of Health and Human Services, Public Health Service. September. Available at http://www.atsdr.cdc.gov/toxprofiles/tp60.html.

ATSDR (Agency for Toxic Substances and Disease Registry). 2004. Interaction Profile for Arsenic, Cadmium, Chromium and Lead. Agency for Toxic Substances and Disease Registry, Atlanta, GA. Available at http://www.atsdr.cdc.gov/interactionprofiles/IP-metals1/ip04.pdf.

ATSDR (Agency for Toxic Substances and Disease Registry). 2006. Interaction Profiles for Toxic Substances. Agency for Toxic Substances and Disease Registry, Atlanta, GA. Available at http://www.atsdr.cdc.gov/interactionprofiles/.

Baghurst, P.A., A.J. McMichael, N.R. Wigg et al. 1992. Environmental exposure to lead and children's intelligence at the age of seven years, The Port Pirie Cohort Study. New Eng. J. Med. 327(18):1279-1284.

Birnbaum, L.S. 1995. Developmental effects of dioxins and other endocrine disrupting chemicals. Neurotoxicology. 16(4):748.

Black, M.R., D.M. Medeiros, E. Brunett et al. 1988. Zinc supplements and serum lipids in young adult white males. Am. J. Clin. Nutr. 47:970-975 (as cited in ATSDR, 2003c).

Bolz, R.E. and G.L. Tuve. 1973. CRC Handbook of Tables for Applied Engineering Science. CRC Press, Cleveland, OH.

Bosch, H.M., A.B. Rosefield, R. Huston, H.R. Shipman and F.L. Woodward. 1950. Methemoglobinemia and Minnesota well supplies. J. Am. Water Works Assoc. 42:161-170 (as cited in U.S. EPA, 2006e).

Boyes, W.K., P.J. Bushnell, K.M. Crofton, M. Evans and J.E. Simmons. 2000. Neurotoxic and pharmacokinetic responses to trichloroethylene as a function of exposure scenario. Environ. Health Perspect. 108(Suppl. 2):317-322.

Brown, R. 1999. Personal communication from R. Brown to M. MacDonell, Argonne National Laboratory, Argonne, IL (for the Hanford groundwater/vadose zone integration project report). November. (as cited in U.S. DOE, 1999).

Bruckner, J.V., W.F. MacKenzie, W. Muralidhara et al. 1986. Oral toxicity of carbon tetrachloride: Acute, subacute and subchronic studies in rats. Fundam. Appl. Toxicol. 6:16-34 (as cited in ATSDR, 2003a).

CCDE (City of Chicago Department of the Environment). 2003. Polynuclear Aromatic Hydrocarbon Background Study: Illinois. Prepared by Tetra Tech EM Inc. under contract to CCDE. February 24.

CDC (Centers for Disease Control and Prevention). 1984. Organophosphate insecticide poisoning among siblings—Mississippi. Morb. Mortal. Wkly. Rep. 33(42):592-594.

CDC (Centers for Disease Control and Prevention). 2006. Third National Report on Human Exposure to Environmental Chemicals. July 2005. Revised February, 2006. Centers for Disease Control and Prevention, Atlanta, GA. NCEH Pub. No. 05-0570. Available at http://www.cdc.gov/exposurereport/.

Cebrian, M.E., A. Albores, M. Aquilar and E. Blakely. 1983. Chronic arsenic poisoning in the north of Mexico. Human Toxicol. 2:121-133 (as cited in U.S. EPA, 2006e).

Chen, J.J., Y.J. Chen, G.E. Rice, K. Hamernik, A. Protzel and R.L. Kodell. 2001. Using dose addition to estimate cumulative risks from exposures to multiple chemicals. Reg. Toxicol. Pharmacol. 34(1):35-41.

Clement, T.P, M.J. Truex and P. Lee. 2002. A case study for demonstrating the application of US EPA's monitored natural attenuation screening protocol at a hazardous waste site. J. Contam. Hydrol. 59(1-2):133-162.

CNN. 2004. Poisoning diagnosis 'rock solid.' CNN World, Dec 12. Available at http://www.cnn.com/2004/WORLD/europe/12/12/yushchenko/index.html.

Cooke, R.M. 1991. Experts in Uncertainty: Opinion and Subjective Probability in Science. Oxford University Press, New York. 321 pp.

Cox, C., T.W. Clarkson, D.O. Marsh et al. 1989. Dose-response analysis of infants prenatally exposed to methyl mercury: An application of a single compartment model to single-strand hair analysis. Environ. Res. 49(2):318-332 (as cited in ATSDR, 1999c).

CPDP (Carcinogenic Potency Database Project). 2004. Summary of Carcinogenic Potency Database by Target Organ (Table 1). Funded by the National Toxicology Program, National Institute of Environmental Health Sciences, U.S. Department of Energy through Lawrence Berkeley National Laboratory, and the University of California at Berkeley. March 23. Available at http://potency.berkeley.edu/pdfs/NCINTPPathology.pdf.

Crump, K.S., T. Kjellstrom, A.M. Shipp, A. Silvers and A. Stewart. 1998. Influence of prenatal mercury exposure upon scholastic and psychological test performance: Benchmark analysis of a New Zealand cohort. Risk Anal. 18(6):701-713.

Cullen, A.C. and H.C. Frey. 1999. Probabilistic Techniques in Exposure Assessment: A Handbook for Dealing with Variability and Uncertainty in Models and Inputs. Plenum Press, New York, NY.

Cutler, J.J., G.S. Parker, S. Rosen, B. Prenney, R. Healey and G.G. Caldwell. 1986. Childhood leukemia in Woburn, Massachusetts. Public Health Rep. 101(2):201-205.

Dawson, B.V., P.D. Johnson, S.J. Goldberg et al. 1993. Cardiac teratogenesis of halogenated hydrocarbon contaminated drinking water. J. Am. Coll. Cardiol. 21:1466-1472 (as cited in ATSDR, 1997c).

DeGroot, M. 1970. Optimal Statistical Decision. McGraw-Hill, New York, NY. 489 pp.

De Oliveira, F.S., M.R. Viana, A.R. Antoniolli et al. 2001. Differential effects of lead and zinc on inhibitory avoidance learning in mice. Braz. J. Med. Biol. Res. 34:117-120 (as cited in ATSDR, 2003c).

DeRosa, C.T., J.F. Stara and P.R. Durkin. 1985. Ranking of chemicals based upon chronic toxicity data. Toxicol. Ind. Health. 1(4):177-192.

Dourson, M.L., S.P. Felter and D. Robinson. 1996. Evolution of science-based uncertainty factors in noncancer risk assessment. Regul. Toxicol. Pharmacol. 24:108-120.

Dourson, M.L., L.K. Teuschler, W.M. Stiteler and P.R. Durkin. 1997. Categorical regression of toxicity data: A case study using aldicarb. Reg. Toxicol. Pharmacol. 25:121-129.

DTSC (Department of Toxic Substances Control). 2003. Johnson and Ettinger (1991) Model for TSC Intrusion into Buildings. Version 3.0-Modification 1. July.

Durant, J.L., J. Chen, H.F. Hemond and W.G. Thilly. 1995. Elevated incidence of childhood leukemia in Woburn, Massachusetts: NIEHS Superfund basic research program searches for causes. Environ. Health Perspect. 103(Suppl. 6):93-98.

E-Doc (Electronic Doctor) Index of Medical Terminology. (c) E-Doc 1998-99. Available at http://www.edoc.co.za/.

Edmond, C., J.E. Michalek, L.S. Birnbaum and M.J. DeVito. 2005. Comparison of the use of a physiologically based pharmacokinetic model and a classical pharmacokinetic model for dioxin exposure assessments. Environ. Health Perspect. 113(12):1666-1668. Available at http://www.ehponline.org/members/2005/8016/8016.html.

EFSA (European Food Safety Authority). 2006. EFSA Colloquium 7 - Cumulative Risk Assessment of pesticides to human health: The way forward. Available at http://www.efsa.europa.eu/en/science/colloquium_series/colloquium_7.html.

EHTPT (Environmental Health Tracking Project Team). 2000. America's Environmental Health Gap: Why the Country Needs a Nationwide Health Tracking Network. Technical Report. Prepared by EHTPT, Johns Hopkins School of Hygiene and Public Health, Department of Health Policy and Management. Sponsored by the Pew Environmental Health Commission. September. Available at http://www.pewtrusts.com/pdf/hhs_enviro_health_gap_technical.pdf.

Elbetieha, A. and M.H. Al-Hamood. 1997. Long-term exposure of male and female mice to trivalent and hexavalent chromium compounds: Effect on fertility. Toxicology. 116:39-47 (as cited in ATSDR, 2000b).

Elder, L., K. Poirier, M. Dourson et al. 2002. Mathematical modeling and quantitative methods. Food Chem. Toxicol. 40:283-326.

Engel, L.S., H. Checkoway, M.C. Keifer et al. 2001. Parkinsonism and occupational exposure to pesticides. Occup. Environ. Med. 58:582-589.

Evans, J.S., J.D. Graham, G.M. Gray and R.L. Sielken Jr. 1994. A distributional approach to characterizing low-dose cancer risk. Risk Anal. 14:25-34.

Farland, W. and M.L. Dourson. 1992. Noncancer Health Endpoints: Approaches to Quantitative Risk Assessment. In: Comparative Environmental Risk Assessment, R. Cothern, Ed. Lewis Publishers Inc., Boca Raton, LA. December.

Feldman, R.G. 1992. Manganese as possible ecoetiologic factor in Parkinson's disease. Ann. New York Acad. Sci. 648:266-267.

Feron, V.J., F.R. Cassee and J.P. Groten. 1998. Toxicology of chemical mixtures: European perspective. Environ. Health Perspect. 106(Suppl. 6):1281-1289.

Ferrario, J.B., C.J. Byrne and D.H. Cleverly. 2000. 2,3,7,8-Dibenzo-*p*-dioxins in mined clay products from the United States: Evidence for possible natural origin. Environ. Sci. Technol. 34:4524-4532.

Fischer, P.W.F., A. Giroux and A.R. L'Abbe. 1984. Effect of zinc supplementation on copper status in adult man. Am. J. Clin. Nutr. 40:743-746 (as cited in ATSDR, 2003c).

Foy, H.M., S. Tarmapai, P. Eamchan et al. 1992. Chronic arsenic poisoning from well water in a mining area in Thailand. Asia Pac. J. Pub. Health. 6(3):150-152 (as cited in ATSDR, 2000a).

Freundt, K.J. and H.A. Ibrahim. 1990. Growth of rats during a subchronic intake of the heavy metals Pb, Cd, Zn, Mn, Cu, Hg, and Be. Pol. J. Occup. Med. 3:227-232 (as cited in ATSDR, 2002a).

Fristachi, A and G. Rice. 2007. Estimating the relative contribution of drinking water to the daily ingestion of N-nitrosodimethylamine (NDMA). J. Water Health. (In Press).

Gierthy, J.F., K.F. Arcaro and M. Floyd. 1997. Assessment of PCB estrogenicity in a human breast cancer cell line. Chemosphere. 34(5-7):1495-1505.

Gilman, A.P., D.C. Villeneuve, V.E. Secours et al. 1998a. Uranyl nitrate: 28-day and 91-day toxicity studies in the Sprague-Dawley rat. Toxicol. Sci. 41(1):117-128 (as cited in ATSDR, 1999d).

Gilman, A.P., D.C. Villeneuve, V.E. Secours et al. 1998b. Uranyl nitrate: 91-day toxicity studies in the New Zealand white rabbit. Toxicol. Sci. 41(1):129-137 (as cited in ATSDR, 1999d).

Gold, L.S., N.B. Manley, T.H. Slone and J.M. Ward. 2001. Compendium of chemical carcinogens by target organ: Results of chronic bioassays in rats, mice, hamsters, dogs, and monkeys. Toxicol. Pathol. 29(6):639-652. Available at http://potency.berkeley.edu/text/ToxicolPathol.pdf.

Gorell, J.M., C.C. Johnson, B.A. Rybicki et al. 1999. Occupational exposure to manganese, copper, lead, iron, mercury and zinc and the risk of Parkinson's disease. Neurotoxicology. 20(2-3):239-248.

Grandjean, P., P. Weihe, R. White et al. 1997. Cognitive deficit in 7-year old children with prenatal exposure to methylmercury. Neurotoxicol. Teratol. 19(6):417-428.

Gunderson, V.M., K.S. Grant-Webster, T.M. Burbacher et al. 1988. Visual recognition memory deficits in methylmercury-exposed *Macaca fascicularis* infants. Neurotoxicol. Teratol. 10(4):373-379 (as cited in ATSDR, 1999c).

Guth, D.J. 1996. Acute exposure response assessment for 1,1,1-trichloroethane using stratified ordinal regression. Presented at the 89th Annual Meeting of the Air and Waste Management Association, Nashville, TN. June 23-28.

Guth, D.J., A.M. Jarabek, L. Wymer and R. Hertzberg. 1991. Evaluation of risk assessment methods for short-term inhalation exposure. Presented at the 84th Annual Meeting of the Air and Waste Management Association, Vancouver, British Columbia. June 16-21.

Guth, D.J., R.J. Carroll, D.G. Simpson et al. 1997. Categorical regression analysis of acute exposure to tetrachloroethylene. Risk Anal. 17(3):321-332.

Guzelian, P.S., M.S. Victoroff, N.C. Halmes, R.C. Janes and C.P. Guzelian. 2005. Evidence-based toxicology: a comprehensive framework for causation. Human Exp. Toxicol. 24:161-201.

Haber, L.T., J.S. Dollarhide, A. Maier and M.L. Dourson. 2001. Noncancer risk assessment: principles and practice in environmental and occupational settings. In: Patty's Toxicology, 5th ed, E. Bingham, B. Cohrssen and C.H. Powell, Ed. Wiley and Sons, Inc., New York, NY. p. 169-232.

Haddad, S., R. Tardif, C. Viau and K. Krishnan. 1999. A modeling approach to account for pharmacokinetic interactions in the calculation of biological hazard index for chemical mixtures. Toxicol. Lett. 108:303–308.

Haddad, S., R. Tardif, C. Viau and K. Krishnan. 2001. A modeling approach to account for toxicokinetic interactions in the calculation of biological hazard index for chemical mixtures. Toxicol. Sci. 63:125–131.

Haines, R.G. 1971. Ingestion of aldicarb by human volunteers: A controlled study of the effect of aldicarb on man. In: EPA Pesticide Petition No. 1F1008. Unpublished report.

Hertzberg, R.C. 1989. Extrapolation and scaling of animal data to humans: Fitting a model to categorical response data with application to species extrapolation of toxicity. Health Phys. 57(Suppl. 1):405-409.

Hertzberg, R.C. and M. Miller. 1985. A statistical model for species extrapolating using categorical response data. Toxicol. Ind. Health. 1(4):43-63.

Hertzberg, R.C. and L. Wymer. 1991. Modeling the severity of toxic effects. Air & Waste Management Association. In: Proceedings papers from the 84th Annual Meeting and Exhibition, June 16-21, 1991, British Columbia. Air and Waste Management Association.

Hertzberg, R.C., G.E. Rice and L.K. Teuschler. 1999. Methods for health risk assessment of combustion mixtures. In: Hazardous Waste Incineration: Evaluating the Human Health and Environmental Risks, S. Roberts, C. Teaf and J. Bean, Ed. CRC Press, Boca Raton, FL. p. 105-148.

Hileman, B. 2001. The environment and Parkinson's. Chem. Eng. News. 79(38). Available at http://www.mindfully.org/Health/Parkinsons-And-Environment.htm.

Hoffman, F.O. and J.S. Hammonds. 1994. Propagation of uncertainty in risk assessments: The need to distinguish between uncertainty due to lack of knowledge and uncertainty due to variability. Risk Anal. 14(5):707-712.

Hoppin, J.A., D.M. Umbach, S.J. London, M.C.R. Alavanja and D.P. Sandler. 2002. Chemical predictors of wheeze among farmer pesticide applicators in the Agricultural Health Study. Am. J. Respir. Crit. Care Med. 165(5):683-689.

Howard, P.H., Ed. 1989. Handbook of Environmental Fate and Exposure Data for Organic Chemicals. Lewis Publishers Inc., Boca Raton, FL.

Hricko, A. 1994. Rings of controversy around benzene. Environ. Health Perspect. 102(3):276-281.

HSDB (Hazardous Substances Data Bank). 1991. Chlorine (CASRN 7782-50-5). National Library of Medicine. Available at http://www.toxnet.nlm.nih.gov/.

HSDB (Hazardous Substances Data Bank). 2006. U.S. National Library of Medicine. Bethesda, MD. Available at http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.

IPCS (International Programme on Chemical Safety). 1998. Environmental Health Criteria 202. Selected non-heterocyclic polycyclic aromatic hydrocarbons. International Programme on Chemical Safety.

IPCS (International Programme on Chemical Safety). 2006. HomePage. World Health Organization. Available at http://www.who.int/ipcs/en/.

IRRST (Institut de reserche Robert-Sauvé en santé et en sécurité du travail). 2003. Mixtures of Substances in Workplaces: A Utility Program for Evaluating the Toxic Risk. Available at http://www.irsst.qc.ca/en/_outil_100024.html.

Johns, D.O., W.E. Daniell, D.D. Shen, D.A. Kalman, R.L. Dills and M.S. Morgan. 2006. Ethanol-induced increase in the metabolic clearance of 1,1,1-trichloroethane in human volunteers. Toxicol. Sci. 92:61-70.

Johnson, P.C. and R.A. Ettinger. 1991. Heuristic model for predicting the intrusion rate of contaminant vapors into buildings. Environ. Sci. Technol. 25:1445-1452.

Jones, N.L., T.P. Clement and C.M. Hansen. 2006. A three-dimensional analytical tool for modeling reactive transport. Ground Water. 44(4):613-617.

Kedderis, G.L. 1997. Extrapolation of *in vitro* enzyme induction data to humans *in vivo*. Chem. Biol. Interact. 107:109-121.

Khan, A.T., A. Atkinson, T.C. Graham et al. 2001. Effects of low levels of zinc on reproductive performance of rats. Environ. Sci. (Tokyo) 8:367-381 (as cited in ATSDR, 2003c).

Khera, K.S. and S.A. Tabacova. 1973. Effects of methylmercuric chloride on the progeny of mice and rats treated before or during gestation. Food Cosmet. Toxicol. 11:245-254 (referenced in ATSDR, 1999c).

Kjellstrom, T., P. Kennedy, S. Wallis et al. 1986. Physical and mental development of children with prenatal exposure to mercury from fish. Stage 1: Preliminary test at age 4. Natl. Swed. Environ. Protec. Bd., Rpt. 3080. (Solna, Sweden)

Kjellstrom, T., P. Kennedy, S. Wallis et al. 1989. Physical and mental development of children with prenatal exposure to mercury from fish. Stage 2: Interviews and psychological tests at age 6. Natl. Swed. Environ. Prot. Bd., Rpt. 3642. (Solna, Sweden)

Kopp, S.J., T. Glonek, H.M. Perry Jr. et al. 1982. Cardiovascular actions of cadmium at environmental exposure levels. Science. 217:837-839 (as cited in ATSDR, 1999b).

Kynast, G. and E. Saling. 1986. Effect of oral zinc application during pregnancy. Gynecol. Obstet. Invest. 21:117-123 (as cited in ATSDR, 2003c).

Lagakos, S.W., B.J. Wessen, M. Aelen. 1986. An analysis of contaminated well water and health effects in Woburn, Massachusetts. J. Am. Stat. Assoc. 81(395):583-596.

Liao, K.H., I.D. Dobrev, J.E. Dennison et al. 2002. Application of biologically-based computer modeling to simple or complex mixtures. Environ. Health Perspect. 110(Suppl. 6):957-963.

Lipscomb, J.C. 2003. How differences in enzyme expression can translate into pharmacokinetic variance and susceptibility to risk. J. Child. Health. 1:189-202.

Lipscomb, J.C. 2004. Evaluating the relationship between variance in enzyme expression and toxicant concentration in health risk assessment. Human Ecol. Risk Assess. 10:39-55.

Mackay, D., W.Y. Shiu, K-C Ma and S.C. Lee. 2006. Physical-Chemical Properties and Environmental Fate for Organic Chemicals. CRC Press, Boca Raton, FL.

MADEP (Massachusetts Department of Environmental Protection). 2002. Technical Update: Background Levels of Polycyclic Aromatic Hydrocarbons and Metals in Soil. Available at http://www.mass.gov/dep/cleanup/laws/orspub03.htm.

Marnicio, R.J., P.J. Hakkinen, S.D. Lutkenhoff, R.C. Hertzberg and P.D. Moskowitz. 1991. Risk analysis software and data bases: Review of Riskware '90 Conference and Exhibition. Risk Anal. 11:545-560.

Martin, S.A., Jr, D.P. Sandler, S.D. Harlow, D.L. Shore, A.S. Rowland and M.C.R. Alavanja. 2002. Pesticide use and pesticide-related symptoms among black farmers in the Agricultural Health Study. Am. J. Ind. Med. 41(3):202-209.

McGuire, T.M., C.J. Newell, B.B. Looney et al. 2004. Historical analysis of monitored natural attenuation: A survey of 191 chlorinated solvent sites and 45 solvent plumes. Remediation. 99:112. Available at http://www.gsi-net.com/Publications/McGuire_HistoricalMNA_pa.pdf.

Mehendale, H.M. 1995. Toxicodynamics of low level toxicant interactions of biological significance: inhibition of tissue repair. Toxicology. 105:251-266.

Miller, F.J., P.M. Schlosser and D.B. Janszen. 2000. Haber's Rule: A special case in a family of curves relating concentration and duration of exposure to a fixed level of response for a given endpoint. Toxicology. 149:20-34.

Morgan, M.G. and M. Henrion. 1990. Uncertainty: A Guide for Dealing with Uncertainty in Quantitative Risk and Policy Analysis. Cambridge University Press, Cambridge, UK.

Morgareidge, K., G.E. Cox and M.A. Gallo. 1976. Chronic feeding studies with beryllium in dogs. Food and Drug Research Laboratories, Inc. Submitted to the Aluminum Company of America, Alcan Research and Development, Ltd., Kawecki-Berylco Industries, Inc., and Brush-Wellman, Inc. (as cited in ATSDR, 2002c).

Mumtaz, M.M., K.A. Poirier and J.T. Coleman. 1997. Risk assessment for chemical mixtures: Fine-tuning the hazard index approach. J. Clean Technol. Environ. Toxicol. Occup. Med. 6(2):189-204.

Myers, G.J., P.W. Davidson, C.F. Shamlaye et al. 1997. Effects of prenatal methylmercury exposure from a high fish diet on developmental milestones in the Seychelles child development study. Neurotoxicology. 18(3):819-289 (as cited in ATSDR, 1999c).

Nadeenko, V.G., V. Lenchenko, S.B. Genkina and T.A. Arkhipenko. 1978. The influence of tungsten, molibdenum, copper and arsenic on the intrauterine development of the fetus. TR-79-0353. Farmakologiya i Toksikologiya. 41:620-623 (as cited in U.S. EPA, 2006e).

Nakashima, M. S. Wu, T. Shigenko et al. 2005. A Field Application of HRC© Bio-Barrier and Subsurface Microorganism Research. Proceedings of the Fourth International Conference on Remediation of Chlorinated and Recalcitrant Compounds (Monterey, CA, May 2004). Battelle Press.

Naranjo, E., F. Hellweger, L.H. Wilson and P. Anid. 2000. Mapping risk from mining activities: A case study of Oruro, Bolivia. Proceedings of the Twentieth Annual ESRI User Conference, June 26-30, San Diego, CA. Available at http://gis.esri.com/library/userconf/proc00/professional/papers/PAP480/p480.htm.

NCHS (National Health and Nutrition Examination Survey). 2002. NHANES 1999-2000 Laboratory Components. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, Hyattsville, MD. Available at http://www.cdc.gov/nchs/data/nhanes/blood.pdf.

Neiger, R.D. and G.D. Osweiler. 1989. Effect of subacute low level dietary sodium arsenite on dogs. Fundam. Appl. Toxicol. 13:439-451 (as cited in ATSDR, 2000a).

Nickel Institute. 1999. Nickel Allergic Contact Dermatitis. Available at http://www.nidi.org/index.cfm/ci_id/99.htm.

Nogawa, K., R. Honda, T. Kido et al. 1989. A dose-response analysis of cadmium in the general environment with special reference to total cadmium intake limit. Environ. Res. 48:7-16 (as cited in ATSDR, 1999b).

NoMiracle (Novel Methods for Integrated Risk Assessment of Cumulative Stressors in Europe). 2006. HomePage. Available at http://nomiracle.jrc.it/default.aspx.

Norris, G., S.N. YoungPong, J.Q. Koenig, T.V. Larson, L. Sheppard and J.W. Stout. 1999. An association between fine particles and asthma emergency department visits for children in Seattle. Environ. Health Perspect. 107(6):489-493.

NPI (National Pollutant Inventory). 2005. Chlorine Fact Sheet. Australian Government, Department of the Environment and Heritage, Canberra, Australia (Oct.). Available at http://www.npi.gov.au/database/substance-info/profiles/20.html.

NRC (National Research Council). 1983. Risk Assessment in the Federal Government: Managing the Process. Committee on the Institutional Means for Assessments of Risk to Public Health, Commission on Life Sciences. National Academy Press, Washington, DC.

NRC (National Research Council). 1994. Science and Judgment in Risk Assessment. Committee on Risk Assessment of Hazardous Air Pollutants, Board on Environmental Sciences and Technology, Commission on Life Sciences. National Academy Press, Washington, DC.

NRC (National Research Council). 2003a. Exposure of the American Population to Radioactive Fallout from Nuclear Weapons Tests: A Review of the CDC-NCI Draft Report on a Feasibility Study of the Health Consequences to the American Population from Nuclear Weapons Tests Conducted by the United States and Other Nations. Board on Radiation Effects Research. National Academy Press, Washington, DC.

NRC (National Research Council). 2003b. A Review of the Dose Reconstruction Program of Defense Threat Reduction Agency (J. Till, Chair). Board on Radiation Effects Research. National Academy Press, Washington, DC.

NRC (National Research Council). 2004. Review of the Army's Technical Guides on Assessing and Managing Chemical Hazards to Deployed Personnel. A report by the Subcommittee on the Toxicological Risks to Deployed Military Personnel, Committee on Toxicology. National Academy Press, Washington, DC.

NRC (National Research Council) 2007. Models in Environmental Regulatory Decision Making. Committee on Models in the Regulatory Decision Process. National Academy Press, Washington, DC. 286 pp.

NTP (National Toxicology Program). 1996. Final Report on the Reproductive Toxicity of Potassium Dichromate (Hexavalent) (CAS No. 7778-50-9) Administered in Diet to SD Rats. NTIS No. PB97-125355. National Institute of Environmental Health Sciences, Research Triangle Park, NC (as cited in ATSDR, 2000b).

NTP (National Toxicology Program). 2002. Report on Carcinogens, 10th ed. U.S. Department of Health and Human Services, Public Health Services, National Institute of Environmental Health Sciences, Washington, DC. December. Available at http://ehp.niehs.nih.gov/roc/toc10.html.

NYSDOH (New York State Department of Health). 2003. Protecting Our Children from Lead: The Success of New York's Efforts to Prevent Childhood Lead Poisoning. January 21. Available at http://www.health.state.ny.us/nysdoh/lead/childlead.pdf.

Öberg, M., A. Sjodin, H. Casabona, I. Nordgren, E. Klasson-Wehler and H. Hakansson. 2002. Tissue distribution and half-lives of individual polychlorinated biphenyls and serum levels of 4-hydroxy-2,3,3',4',5-pentachlorobiphenyl in the rat. Toxicol. Sci. 70(2):171-182.

O'Connor, G.T. and D.R. Gold. 1999. Cockroach allergy and asthma in a 30-year-old man. Environ. Health Perspect. 107(3):243-247. March. Available at http://ehp.niehs.nih.gov/members/1999/107p243-247oconnor/oconnor-full.html.

OMB (Office of Management and Budget). 2006. Proposed Risk Assessment Bulletin. Washington, DC. Available at http://www.whitehouse.gov/omb/inforeg/proposed_risk_assessment_bulletin_010906.pdf.

Parker, G.S. and S.L. Rosen. 1981. Woburn: Cancer Incidence and Environmental Hazards, 1969-1978. Massachusetts Department of Public Health. Available at http://www.sph.umich.edu/geomed/grabber/1981ca.pdf.

Paulu, C., A. Aschengrau and D. Ozonoff. 2002. Exploring associations between residential location and breast cancer in a case-control study. Environ. Health Perspect. 110(5):471-478.

Perera, F.P., V. Rauh, W-Y. Tsai et al. 2003. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multi-ethnic population. Environ. Health Perspect. 111:201–205.

Perera, F., D. Tang, Y.-H. Tu et al. 2004. Biomarkers in maternal and newborn blood indicate heightened fetal susceptibility to procarcinogenic DNA Damage. Environ. Health Perspect. 112:1133-1136.

Perry, H.M. Jr., M.W. Erlanger, T.O. Gustafsson et al. 1989. Reversal of cadmium-induced hypertension by D-myo-inositol-1,2,6-trisphosphate. J. Toxicol. Environ. Health 28:151-159 (as cited in ATSDR, 1999b).

Peterson, D.E., M.S. Kanarek, M.A. Kuykendall et al. 1995. Fish consumption patterns and blood mercury levels in Wisconsin Chippewa Indians. Arch. Environ. Health. 49(1):53-58.

Pohl, H.R. and H.G. Abadin. 1995. Utilizing uncertainty factors in minimal risk levels derivation. Regul. Toxicol. Pharmacol. 22:180-188.

Pohl, H.R., N. Roney, S. Wilbur, H. Hansen and C.T. DeRosa. 2003. Six interaction profiles for simple mixtures. Chemosphere. 53:183-197.

Public Health Service. 1981. Cancer in Woburn, Massachusetts. EPI-80-37-2. Centers for Disease Control and Prevention, Atlanta, GA.

RAIS (Risk Assessment Information System). 1991. Toxicity Summary for Cadmium. Updated 8/29/97, accessed September 2003. Available at http://risk.lsd.ornl.gov/index.shtml.

RAIS (Risk Assessment Information System). 1995. Toxicity Summary for Nitrate. Accessed September 2003. Available at http://risk.lsd.ornl.gov/index.shtml.

Rao, V.R., K. Levy and M. Lustik. 1993. Logistic regression of inhalation toxicities of perchloroethylene - Application in noncancer risk assessment. Reg. Toxicol. Pharmacol. 18:233-247.

Regoli, F., M. Nigro, M. Benedetti et al. 2005. Interactions between metabolism of trace metals and xenobiotic agonists of the aryl hydrocarbon receptor in the antarctic fish Trematomus bernacchii: environmental perspectives. Environ. Toxicol. Chem. 24(6):1475-1482.

Richardson, J.P. 2004. Monitoring, education and partnerships through the Georgia Southeast and Coastal Region Training Center. Poster presented at the 2004 National Monitoring Conference, Chattanooga, TN, May 17-20. Available at http://water.usgs.gov/wicp/acwi/monitoring/conference/2004/.

Santucci, B, R. Manna F and C. Cannistraci et al. 1994. Serum and urine concentrations in nickel-sensitive patients after prolonged oral administration. Contact Dermatitis. 30:97-101 (as cited in ATSDR, 2003b).

Schroeder, H.A. and M. Mitchener. 1975. Life-term studies in rats: Effects of aluminum, barium, beryllium,and tungsten. J. Nutr. 105:421-427 (as cited in ATSDR, 2002c).

Schroeder, H.A., J.J. Balassa and W.H. Vinton Jr. 1965. Chromium, cadmium and lead in rats: Effects on lifespan, tumors and tissue levels. J. Nutr. 86:51-66 (as cited in ATSDR, 2000b).

Sette, W.F. 1992. Memorandum: Joint OPPT/OW/ORD Review of 1992 Aldicarb Human Study. U.S. Environmental Protection Agency, Washington, DC. Sept. 4, 1992.

Shiwen, C., Y. Lin, H. Zhineng et al. 1990. Cadmium exposure and health effects among residents in an irrigation area with ore dressing wastewater. Sci. Total Environ. 90:67-73 (as cited in ATSDR, 1999b).

Shuval, H.I. and N. Gruener. 1972. Epidemiological and toxicological aspects of nitrates and nitrites in the environment. Am. J. Public Health. 62(8):1045-1052 (as cited in RAIS, 1995).

Simmons, J.E., S.D. Richardson, T.F. Speth et al. 2002. Development of a research strategy for integrated technology-based toxicological and chemical evaluation of complex mixtures of drinking water disinfection byproducts. Environ. Health Perspect. 110(6):1013-1024.

Simon, C., H. Manzke, H. Kay and G. Mrowetz. 1964. Occurrence, pathogenesis, and possible prophylaxis of nitrite induced methemoglobinemia. Zeitschr. Kinderheilk. 91:124-138 (German) (as cited in U.S. EPA, 2006e).

Simon, T.W. 1999. Two dimensional Monte Carlo simulation and beyond: A comparison of several probabilistic risk assessment methods applied to a Superfund site. Human Ecol. Risk Assess. 5(4):823-843.

Soni, M.G., S.K. Ramaiah, H. Mumtaz, H.M. Clewell and H. Mehendale. 1999. Toxicant-inflicted injury and stimulated tissue repair are opposing toxicodynamic forces in predictive toxicology. Regul. Toxicol. Pharmacol. 29:165-174.

Stange, A.W., D.E. Hilmas, F.J. Furman and T.R. Gatliffe. 2001. Beryllium sensitization and chronic beryllium disease at a former nuclear weapons facility. Appl. Occup. Environ. Hyg. 16(3):405-417.

Stayner, L., A.J. Bailer, R. Smith, S. Gilbert, F. Rice and E. Kuempel. 1999. Sources of uncertainty in dose-response modeling of epidemiological data for cancer risk assessment. Ann. NY Acad. Sci. 895:212-222.

Stephenson, J. 2000. Exposure to home pesticides linked to Parkinson's disease. J. Am. Med. Assoc. 283(23):3055-3056.

Strickland, J.A. and D.J. Guth. 2002. Quantitative exposure-response assessment approaches to evaluate acute inhalation toxicity of phosgene. Human Ecol. Risk Assess. 8(3):511-536.

Susser, M. 1991. Philosophy in epidemiology. Theor. Med. 12(3):271-273.

Suter, G.W. 1999. Developing conceptual models for complex ecological risk assessments. Hum. Ecol. Risk Assess. 5:375-396.

Suter, G.W., T. Vermeire, W.R. Munns Jr. and J. Sekizawa. 2003. Framework for the integration of health and ecological risk assessment. Hum. Ecol. Risk Assess. 9:281-301.

Swartout, J.C., P.S. Price, M.L. Dourson, H.L. Carlson-Lynch and R.E. Keenan. 1998. A probabilistic framework for the reference dose (probabilistic RfD). Risk Anal. 18(3):271-282.

TCEQ (Texas Commission on Environmental Quality). 1999. Texas-Specific Background Concentrations, Texas Risk Reduction Program (TRRP) Rule, Figure: 30 TAC Section 350.51(m), September 2. Available at http://www.tceq.state.tx.us/assets/public/remediation/trrp/350revisions.doc.

TCEQ (Texas Commission on Environmental Quality). 2002. Risk Levels, Hazard Indices, and Cumulative Adjustment, Texas Natural Resource Conservation Commission (TNRCC) Regulatory Guidance, Remediation Division, RG-366/TRRP-18, August. Available at http://www.tceq.state.tx.us/.

TCEQ (Texas Commission on Environmental Quality). 2003. Texas Risk Reduction Program (TRRP) Rule Protective Concentration Level (PCL) Tables, Chemical/Physical Properties. March. Available at http://www.tnrcc.state.tx.us/permitting/trrp.htm.

Telles, N.C. 1981. Cancer Mortality in Woburn – A Three-Decade Study (1949-1978). Massachusetts Department of Public Health.

Teuschler, L.K., M.L. Dourson, W.M. Stiteler, P. McClure and H. Tully. 1999. Health risk above the reference dose for multiple chemicals. Reg. Toxicol. Pharmacol. 30:S19-S26.

Teuschler, L.K., G.E. Rice, C.R. Wilkes, J.C. Lipscomb and F.W. Power. 2004. A feasibility study of cumulative risk assessment methods for drinking water disinfection by-product mixtures. J. Toxicol. Environ. Health A. 67:755-777.

The New Lexicon: Webster's Dictionary of the English Language. 1989. Lexicon Publications, Inc., New York, NY.

The On-line Medical Dictionary (c) Academic Medical Publishing & CancerWEB 1997-98. Distributed by CancerWEB under license from Academic Medical Publishing. Accessed July-September 2001. Available at http://www.betterhealth.vic.gov.au/bhcv2/bhcsite.nsf/pages/bhc_medicaldictionary?opendocument.

Toy, K.A., G.D. Gawne-Mittelstaedt, N.L. Pollisar and S. Liao. 1995. A Fish Consumption Survey of the Tulalip and Squaxin Island Tribes of Puget Sound. Report to Tulalip Tribes, Department of the Environment. Seattle, WA.

TOXNET (Toxicology Data Network). 2005. Tetrachloroethylene. National Library of Medicine. Available at http://toxnet.nlm.nih.gov/ (accessed 2006).

Tucker, A.N., V.M. Sanders, D.W. Barnes et al. 1982. Toxicology of trichloroethylene in the mouse. Toxicol. Appl. Pharmacol. 62:351-357 (as cited in ASTDR, 1997c).

U.S. Consumer Product Safety Commission. 2005. Interim Enforcement Policy Lead Levels. Washington, DC. Available at http://www.cdc.gov/nceh/lead/ACCLPP/Mar%202005/Docs/03%20-%20Interim%20Policy%20Lead%20Levels-Kristina%20Hatlelid.pdf.

U.S. DOE (Department of Energy). 1999. Risk/Impact Technical Report for the Hanford Groundwater/Vadose Zone Integration Project. Prepared by Argonne National Laboratory for U.S. Department of Energy Center for Risk Excellence, Argonne, IL. January. DOE/CH/CRE-7-1999.

U.S. DOE (Department of Energy). 2005. Natural Attenuation Monitor. Prepared by SRNL for U.S. Department of Energy, Savannah River Site, GA. Issue 3, March. (This work at the Savannah River Site is also highlighted at http://www.epa.gov/ada/highlights/jan2006_highlights.html.)

U.S. EPA. 1980. Guidelines and Methodology Used in the Preparation of Health Effect Assessment Chapters of the Consent Decree Water Criteria Documents. Fed. Reg. 45(231):79347-79357.

U.S. EPA. 1981. Ambient Water Quality Criteria Document: Chlorine. U.S. Environmental Protection Agency, Washington, DC. EPA 450/3-78-005. (as cited by HSDB, 1991; accessed 2006).

U.S. EPA. 1985. Guideline for Determination of Good Engineering Practice Stack Height (Technical Support Document for the Stack Height Regulations) – Revised. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Research Triangle Park, NC. June. EPA/450/4-80/023R.

U.S. EPA. 1986a. Guidelines for the Health Risk Assessment of Chemical Mixtures. U.S. Environmental Protection Agency, Office of Research and Development, Washington, DC. September. EPA/630/R-98/002.

U.S. EPA. 1986b. Guidelines for Carcinogen Risk Assessment. Fed. Reg. 51(185):33992-34003.

U.S. EPA. 1987. The Risk Assessment Guidelines of 1986. U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Washington, DC. EPA/600/8-87/045.

U.S. EPA. 1989a. Risk Assessment Guidance for Superfund: Volume 1, Human Health Evaluation Manual (Part A). U.S. Environmental Protection Agency, Office of Emergency and Remedial Response, Washington, DC. EPA/540/1-89/002. (Also see Parts B-D.)

U.S. EPA. 1989b. Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Dibenzo-*p*-dioxins and -dibenzofurans (CDDs and CDFs) and 1989 Update. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC. EPA/625/3-89/016.

U.S. EPA. 1991a. Guidelines for Developmental Toxicity Risk Assessment. Federal Register. 56(234):63798-63826.

U.S. EPA. 1991b. Drinking Water Criteria Document for PAH. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC.

U.S. EPA. 1992a. Guidelines for Exposure Assessment. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC. EPA/600/Z-92/001.

U.S. EPA. 1992b. Screening Procedures for Estimating the Air Quality Impact of Stationary Sources, Revised. Office of Air Quality Planning and Standards, Research Triangle Park, NC. October. EPA/454/R-92/019.

U.S. EPA. 1994a. Revised Interim Soil Lead Guidance for CERCLA Sites and RCRA Corrective Action Facilities. U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, DC. OSWER Directive #9355.4-12.

U.S. EPA. 1994b. Chemical Summary for Chlorine. Office of Pollution Prevention and Toxics, Washington, DC. EPA/749/F-94/010a, Available at http://www.epa.gov/chemfact/s_chlori.txt.

U.S. EPA. 1995a. Profile of the Metal Mining Industry. U.S. Environmental Protection Agency, Office of Compliance, Office of Enforcement and Compliance Assurance, Washington, DC. September. EPA/310/R-95/008. Available at http://www.epa.gov/compliance/resources/publications/assistance/sectors/notebooks/metminsnpt1.pdf.

U.S. EPA. 1995b. Policy for Risk Characterization. Memorandum from Agency Administrator Carol M. Browner, Washington, DC. March 21.

U.S. EPA. 1995c (et sequelae). Compilation of Air Pollutant Emission Factors. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. EPA AP-42. Available at http://www.epa.gov/ttn/chief/ap42/.

U.S. EPA. 1996a. Soil Screening Guidance, Technical Background Document. U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, DC. May. EPA/540/R-95/128. Available at http://www.epa.gov/superfund/resources/soil/introtbd.htm.

U.S. EPA. 1996b. PCBs: Cancer Dose-Response Assessment and Application to Environmental Mixtures. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington Office, Washington, DC. EPA/600/P-96/001F.

U.S. EPA. 1997a. Guidance on Cumulative Risk Assessment, Part 1. Planning and Scoping. U.S. Environmental Protection Agency, Science Policy Council, Washington, DC. Attachment to memo dated July 3, 1997 from the Administrator, Carol Browner, and Deputy Administrator, Fred Hansen, titled "Cumulative Risk Assessment Guidance-Phase I Planning and Scoping." Available at http://www.epa.gov/OSA/spc/2cumrisk.htm.

U.S. EPA. 1997b. Chemical and Radiation Leukemogenesis in Humans and Rodents and the Value of Rodent Models for Assessing Risks of Lymphohematopoietic Cancers. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington, DC. May. EPA/600/R-97/090. Available at http://www.epa.gov/ncea/pdfs/lympho.pdf.

U.S. EPA. 1997c. Exposure Factors Handbook – Volumes I, II, and III (General Factors, Food Ingestion Factors, and Activity Factors). U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington, DC. August. EPA/600/P-95/002Fa. Available at http://www.epa.gov/ncea/pdfs/efh/front.pdf.

U.S. EPA. 1997d. Research on Risk Assessment Issues with Commercial Mixtures Using Toxaphene as a Case Study. U.S. Environmental Protection Agency, National Center for Environmental Assessment, Cincinnati, OH.

U.S. EPA. 1997e. Mercury Study Report to Congress. U.S. Environmental Protection Agency, Office of Research and Development, Office of Air Quality, Planning & Standards, Washington, DC. EPA/452/R-97/003.

U.S. EPA. 1997f. Guiding Principles for Monte Carlo Analysis. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC. EPA/630/R-97/001.

U.S. EPA. 1998a. Methodology for Assessing Health Risks Associated with Multiple Pathways of Exposure to Combustor Emissions. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. December. EPA/600/R-98/137.

U.S. EPA. 1998b. Guidelines for Neurotoxicity Risk Assessment. Federal Register. 63(93): 26926-26954. EPA/630/R-95/001F.

U.S. EPA. 1998c. Guidelines for Ecological Risk Assessment. Federal Register. 63(93): 26846-26924. EPA/630/R-95/002F.

U.S. EPA. 1998d. C x T: Historical perspectives, current issues, and approaches. In: Summary of the U.S. EPA Workshop on the Relationship Between Exposure Duration and Toxicity. U.S. Environmental Protection Agency, National Center for Environmental Assessment, Washington, DC. September. EPA/600/R-99/081.

U.S. EPA. 1998e. Handbook for Air Toxics Emission Inventory Development, Volume I: Stationary Sources. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Office of Air and Radiation, Washington, DC. EPA/454/B-98/002.

U.S. EPA. 1999a. Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity. U.S. Environmental Protection Agency, Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1999b. A Guide to Preparing Superfund Proposed Plans, Records of Decision, and Other Remedy Selection Decision Documents: 6.0: Writing the Record of Decision. U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, DC. EPA/540/R-98/031.

U.S. EPA. 1999c. Sociodemographic Data Used for Identifying Potentially Highly Exposed Populations. U.S. Environmental Protection Agency, National Center for Environmental Assessment, Washington, DC. July. EPA/600/R-99/060. Summary information (not the report) is available at http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=428679.

U.S. EPA. 1999d. Reregistration Eligibility Decision Facts for Chlorine Gas. U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Washington, DC. February. EPA/738/F-99/001. Available at http://www.epa.gov/oppsrrd1/REDs/factsheets/4022fact.pdf.

U.S. EPA. 1999e. Guidance for Performing Aggregate Exposure and Risk Assessments. U.S. Environmental Protection Agency, Office of Pesticide Programs, Washington, DC. October. Available at http://www.pestlaw.com/x/guide/1999/EPA-19991029A.html.

U.S. EPA. 1999f. Screening Level Ecological Risk Assessment Protocol for Hazardous Waste Combustion Facilities. Peer Review Draft. U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, DC. EPA/R6-098/002A. November. Available at http://www.epa.gov/epaoswer/hazwaste/combust/ecorisk.htm.

U.S. EPA. 1999g. Frequently Asked Questions (FAQs) on the Adult Lead Model. Technical Review Workgroup for Lead Guidance Document. U.S. Environmental Protection Agency, Washington, DC. April.

U.S. EPA. 1999h. Handbook for Criteria Pollutant Inventory Development: A Beginner's Guide for Point and Area Sources. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Office of Air and Radiation, Washington, DC. September. EPA/454/R-99/037.

U.S. EPA. 1999i. Risk Assessment Guidance for Superfund (Volume 3, Part A: Process for Conducting Probabilistic Risk Assessment). Draft. U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, DC. December. Available at http://www.epa.gov/oswer/riskassessment/rags3adt/.

U.S. EPA. 2000a. Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC. EPA/630/R-00/002. Available at http://www.epa.gov/ncea/raf/pdfs/chem_mix/chem_mix_08_2001.pdf.

U.S. EPA. 2000b. Community Risk-Based Air Screening: A Case Study in Baltimore, MD. Baltimore Community Environmental Partnership, Air Committee Technical Report. U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC. April. EPA/744/R-00/005.

U.S. EPA. 2000c. CATREG Software Documentation. Office of Research and Development, Washington, DC. EPA/600/R-98/053F.

U.S. EPA. 2000d. CATREG Software User Manual. Office of Research and Development, Washington, DC. EPA/600/R-98/052F.

U.S. EPA. 2000e. Conducting a Risk Assessment of Mixtures of Disinfection By-Products (DBPs) for Drinking Water Treatment Systems. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. EPA/600/R-03/040.

U.S. EPA. 2000f. Science Policy Council Handbook: Risk Characterization. U.S. Environmental Protection Agency, Science Policy Council, Washington, DC. EPA/100/B-00/002.

U.S. EPA. 2000g. Guidance for the Data Quality Objectives Process (QA/G-4). U.S. Environmental Protection Agency, Washington, DC. Available at http://www.epa.gov/quality/qs-docs/g4-final.pdf.

U.S. EPA. 2000h. Guidance for Data Quality Assessment: Practical Methods for Data Analysis. U.S. Environmental Protection Agency, Office of Environmental Information, Washington, DC. July. EPA/600/R-96/084. Available at http://www.epa.gov/region10/www/offices/oea/epaqag9.pdf.

U.S. EPA. 2000i. Trichloroethylene: Hazard Summary. Technology Transfer Network Air Toxics Website, Created in April 1992; Revised in January 2000. Office of Air and Radiation, Washington, DC. Available at http://www.epa.gov/ttn/uatw/hlthef/tri-ethy.html.

U.S. EPA. 2001a. General Principles for Performing Aggregate Exposure and Risk Assessments. U.S. Environmental Protection Agency, Office of Pesticide Programs, Washington, DC. Fax-On-Demand. Fax no. (202) 401-0527. Item no. 6043.

U.S. EPA. 2001b. Methylmercury Reference Dose. Integrated Risk Information System. Available at http://www.epa.gov/iris/subst/0073.htm.

U.S. EPA. 2001c. Risk Assessment Guidance for Superfund. Vol. I. Human Health Evaluation Manual (Part D), Standardized Planning, Reporting, and Review of Superfund Risk Assessments. U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 2001d. Guidance for Characterizing Background Chemicals in Soil at Superfund Sites. External Review Draft. U.S. Environmental Protection Agency, Washington, DC. June. EPA/540/R-01/003.

U.S. EPA. 2001e. Risk Assessment Guidance for Superfund. Vol. 3, Part A: Process for Conducting Probabilistic Risk Assessment (RAGS 3A). U.S. Environmental Protection Agency, Office of Emergency and Remedial Response, Washington, DC. EPA/540/R-02/002.

U.S. EPA. 2001f. Workshop on Approaches to Polycyclic Aromatic Hydrocarbon (PAH) Health Assessment. Discussion document. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington, DC. NCEA-3-1105.

U.S. EPA. 2002a. Organophosphate Pesticides: Revised Cumulative Risk Assessment. U.S. Environmental Protection Agency, Office of Pesticide Programs, Washington, DC. Available at http://www.epa.gov/pesticides/cumulative/rra-op/.

U.S. EPA. 2002b. Region/ORD Workshop on Cumulative Risk Assessment. November 4-8, 2002, Dallas, TX. Office of Science Policy, Washington, DC. Available at http://www.epa.gov/osp/regions/cmrskrpt.pdf.

U.S. EPA. 2002c. Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity. U.S. Environmental Protection Agency, Office of Pesticide Programs, Washington, DC. Available at http://www.epa.gov/oppfead1/trac/science/cumulative_guidance.pdf.

U.S. EPA. 2002d. Ground Water and Drinking Water Technical Fact Sheet on 1,1-Dichloroethylene. U.S. Environmental Protection Agency, Office of Ground Water and Drinking Water, Washington, DC. November. Available at http://www.epa.gov/OGWDW/dwh/t-voc/11-dichl.html.

U.S. EPA. 2002e. A Review of the Reference Dose and Reference Concentration Processes. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC. EPA/630/P-02/002F. Available at http://epa.gov/iriswebp/iris/RFD_FINAL[1].pdf.

U.S. EPA. 2002f. Lessons Learned on Planning and Scoping of Environmental Risk Assessment. Memorandum from Science Policy Council. January. Available at http://www.epa.gov/osp/spc/llmemo.htm.

U.S. EPA. 2002g. Region 9 Preliminary Remediation Goals Table 2002 Update. Technical Memorandum (from Stanford Smucker, Regional Toxicologist, to PRG Table Users). U.S. Environmental Protection Agency, Washington, DC. October. Available at http://www.epa.gov/region09/waste/sfund/prg/files/02userguide.pdf.

U.S. EPA. 2002h. Guidance for Evaluating the Vapor Intrusion to Indoor Air Pathway from Groundwater and Soils (subsurface vapor intrusion guidance). Draft. Federal Register. 67(230):71169-71172. November 29. Available at http://www.epa.gov/correctiveaction/eis/vapor.htm.

U.S. EPA. 2002i. Child-Specific Exposure Factors Handbook. Interim Report. U.S. Environmental Protection Agency, National Center for Environmental Assessment, Washington, DC. EPA/600/P-00/02b. Available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55145.

U.S. EPA. 2002j. Guidance on Environmental Data Verification and Data Validation. Office of Environmental Information, Washington, DC. EPA/240/R 02/004. Available at http://www.epa.gov/quality/qs-docs/g8-final.pdf.

U.S. EPA. 2002k. Groundwater and Ecosystems Restoration Research. Biochlor Version 2.2. March 2002. Available at http://www.epa.gov/ada/csmos/models/biochlor.html (last updated March 2006).

U.S. EPA. 2003a. Framework for Cumulative Risk Assessment. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington, DC. EPA/600/P-02/001F. Available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=54944.

U.S. EPA. 2003b. The Feasibility of Performing Cumulative Risk Assessments for Mixtures of Disinfection By-Products in Drinking Water. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. EPA/600/R-03/051.

U.S. EPA. 2003c. Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds. National Academy Sciences (NAS) Review Draft. U.S. Environmental Protection Agency, Exposure Assessment and Risk Characterization Group, Washington, DC. EPA/600/P-00/001Cb.

U.S. EPA. 2003d. Guideline on Air Quality Models, Appendix W of CFR Part 51, April. Available at http://www.arb.ca.gov/toxics/harp/docs/40CFR_APPW.pdf.

U.S. EPA. 2003e. Considerations in Risk Communication: A Digest of Risk Communication as a Risk Management Tool. U.S. Environmental Protection Agency, National Risk Management Research Laboratory, Cincinnati, OH. March. EPA/625/R-02/004. Available at http://www.epa.gov/ORD/NRMRL/Pubs/625r02004/625r02004.pdf.

U.S. EPA. 2003f. Developing Relative Potency Factors for Pesticide Mixtures: Biostatistical Analyses of Joint Dose-Response. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. EPA/600/R-03/052. Available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=66273.

U.S. EPA. 2003g. Guidance for Developing Ecological Soil Screening Levels. Revised February 2005. U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, DC. OSWER Directive 9285.7-55. Available at http://www.epa.gov/ecotox/ecossl/pdf/ecossl_guidance_chapters.pdf.

U.S. EPA. 2003h. Region/ORD Workshop on Inhalation Risk Assessment: A Superfund Focus: Summary Report. U.S. Environmental Protection Agency, Washington, DC. September 9-12, 2003. Available at http://intranet.epa.gov/ospintra/scienceportal/htm/complete.htm#inhale.

U.S. EPA. 2003i. Region 3 Risk-Based Concentrations (RBC) Tables. Technical Background Document (from Jennifer Hubbard, Regional Toxicologist, to RBC Table Users). U.S. Environmental Protection Agency, Washington, DC. October. Available at http://www.epa.gov/reg3hwmd/risk/human/info/cover.pdf.

U.S. EPA. 2003j. User's Guide for Evaluating Subsurface Vapor Intrusion into Buildings. Draft. Prepared by Environmental Quality Management under Contract #68-W-01-058 to U.S. Environmental Protection Agency, Office of Emergency and Remedial Response, Washington DC. June 19. Available at http://www.epa.gov/superfund/programs/risk/airmodel/guide.pdf.

U.S. EPA. 2003k. Draft Guidance on the Development, Evaluation, and Application of Regulatory Environmental Models. Council on Regulatory Models, Office of Science Policy, Office of Research and Development, Washington, DC.

U.S. EPA. 2004a. Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment). U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, DC. EPA/540/R/99/005. Available at http://www.epa.gov/oswer/riskassessment/ragse/.

U.S. EPA. 2004b. Framework for Inorganic Metals Risk Assessment. U.S. Environmental Protection Agency, Office of Research and Development, Risk Assessment Forum, Washington, DC. EPA/630/P-04/068B.

U.S. EPA. 2004c. Air Screening Assessment for Cook County Illinois and Lake County Indiana. Prepared by Argonne National Laboratory, Argonne, IL, in support of the U.S. EPA Region V Cumulative Risk Initiative, for U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics and Region V. (In press.)

U.S. EPA. 2004d. Human Exposure Measurements: National Human Exposure Assessment Survey (NHEXAS). Office of Research and Development, National Exposure Research Laboratory. Accessed March 2004. Available at http://www.epa.gov/heasd/edrb/nhexas.htm.

U.S. EPA. 2004e. Air Quality Criteria for Particulate Matter. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Research Triangle Park, NC. EPA/600/P-99/002aF. Available at http://cfpub.epa.gov/ncea/cfm/partmatt.cfm.

U.S. EPA. 2004f. Health-based Short-term Advisory Levels: Pilot Guide. National Homeland Security Research Center, Cincinnati, OH.

U.S. EPA. 2004g. Benchmark Dose Software. U.S. Environmental Protection Agency, Washington, DC. Accessed February 18. Available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20167.

U.S. EPA. 2004h. Supplemental Guidance for Dermal Risk Assessment, Part E of Risk Assessment Guidance for Superfund, Human Health Evaluation Manual (Volume I). Memorandum from M.B. Cook (Director, Office of Superfund Remediation and Technology Innovation, Washington, DC) to Superfund National Policy Managers and Regional Toxics Integration Coordinators, Regions 1-10. OSWER 9285.7 02 EP (Aug. 16). Available at http://www.epa.gov/oswer/riskassessment/ragse/pdf/part_e_impl_2004_final.pdf.

U.S. EPA. 2005a. Wells G & H Fact Sheet. U.S. Environmental Protection Agency, Region 1, Boston, MA. Available at http://www.epa.gov/NE/superfund/sites/wellsgh/factsh.html.

U.S. EPA. 2005b. Human Health Risk Assessment Protocol for Hazardous Waste Combustion Facilities, Final. U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response (5305W), Washington, DC. EPA/520/R-05/006. Available at http://www.epa.gov/epaoswer/hazwaste/combust/risk.htm.

U.S. EPA. 2005c. Human Health Medium-Specific Screening Levels. U.S. Environmental Protection Agency, Region 6, Dallas, TX. November. Available at http://www.epa.gov/earth1r6/6pd/rcra_c/pd-n/r6screenbackground.pdf.

U.S. EPA. 2005d. Guidelines for Carcinogen Risk Assessment. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC. EPA/630/P-03/001B.

U.S. EPA. 2005e. Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC. EPA/630/R-03/003F.

U.S. EPA. 2005f. All-Ages Lead Model (AALM) Version 1.05 (External Review Draft). U.S. Environmental Protection Agency, Washington, DC. EPA/600/C-05/013. Available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=139314.

U.S. EPA. 2005g. Technical Support Document for the Final Clean Air Mercury Rule: Air Quality Modeling. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Research Triangle Park, NC.

U.S. EPA. 2006a. Office of Water: Protocol for Developing Sediment Total Maximum Daily Load (TMDL): Glossary. Terminology Reference System. U.S. Environmental Protection Agency, Washington, DC. Available at http://iaspub.epa.gov/trs/trs_proc_qry.alphabet?p_term_nm=V&p_reg_auth_id=1&p_data_id=11570&p_version=1.

U.S. EPA. 2006b. Technical Factsheet on: Chlordane. U.S. Environmental Protection Agency, Office of Water, Office of Ground Water and Drinking Water, Washington, DC. Available at http://www.epa.gov/safewater/dwh/t-soc/chlordan.html (last updated Feb. 28, 2006).

U.S. EPA. 2006c. Technical Factsheet on 1,1-Dichloroethylene. U.S. Environmental Protection Agency, Office of Water, Office of Ground Water and Drinking Water, Washington, DC. Available at http://www.epa.gov/safewater/dwh/c-voc/11-dichl.html (last updated Feb. 28, 2006).

U.S. EPA. 2007. Integrated Risk Information System (IRIS). U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available at www.epa.gov/iris.

Verma, A.K., G.T. Bryan and C.A. Reznikoff. 1985. Tumor promoter 12-O-tetradecanoylphorbol-13-acetate receptors in normal human transitional epithelial cells. Carcinogenesis. 6(3):427-432.

Vogel, T.M. and P.L. McCarty. 1985. Biotransformation of tetrachloroethylene to trichloroethylene, dichloroethylene, vinyl chloride, and carbon dioxide under methanogenic conditions. Appl. Environ. Microbiol. 49(5):1080-1083.

Waller, K., S.H. Swan, G. DeLorenze and B. Hopkins. 1998. Trihalomethanes in drinking water and spontaneous abortion. Epidemiology. 9(2):134-140.

Walton, G. 1951. Survey of literature relating to infant methemoglobinemia due to nitrate-contaminated water. Am. J. Public Health. 41:986-996 (as cited in U.S. EPA, 2006e).

Weischer, C.H., W. Kordel and D. Hochrainer. 1980. Effects of NiCl2 and NiO in Wistar rats after oral uptake and inhalation exposure, respectively. Zent Bakteriol. Mikrobiol. Hyg. (B) 171:336-351 (as cited in ATSDR, 2003b).

WHO (World Health Organization). 1996. Chlorine in Drinking-water: Background Document for Development of WHO Guidelines for Drinking-water Quality. World Health Organization, Geneva. Available at http://www.who.int/water_sanitation_health/dwq/chlorine.pdf.

Wright, J.M. and J. Keller-Byrne. 2005. Environmental determinants of Parkinson's Disease. Arch. Environ. Occup. Health. 60(1):32-38.

Wyld, P.J., C.E. Watson, W.S. Nimmo and N. Watson. 1992. A Safety and Tolerability Study of Aldicarb at Various Dose Levels in Healthy Male and Female Volunteers. Study submitted to U.S. EPA by Rhone-Poulenc Company (as summarized by Sette, 1992).

Yadrick, M.K., M.A. Kenney and E.A. Winterfeldt. 1989. Iron, copper, and zinc status: Response to supplementation with zinc or zinc and iron in adult females. Am. J. Clin. Nutr. 49:145-150 (as cited in U.S. EPA, 2006e).

Zhang, J. and X. Li. 1987. Chromium pollution of soil and water in Jinzhou. J. Chinese Prev. Med. 21:262-264 (as cited in ATSDR, 2000b).

Zwart, A. and R.A. Woutersen. 1988. Acute inhalation toxicity of chlorine in rats and mice: Time-concentration-mortality relationships and effects on respiration. J. Haz. Mat. 19:195-208.

7. GLOSSARY

Important terms used in this 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 document 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 EPA 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 document.) 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.)

Initiating factor. 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.

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 EPA 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 this is 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 document 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.

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 EPA and U.S. DOE. Many of these resources are also useful for other types of cumulative risk analyses, and tools from EPA studies for several regulatory programs are also included here. In addition to resources provided by the EPA, included herein are many documents from other Federal Agencies and organizations. They are included to provide sources of information to the reader that may be useful in conducting a cumulative risk assessment, however, their inclusion does not necessarily imply their review or endorsement by the EPA.

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 the 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 document, 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 EPA Office of Science Policy, Science Policy Council, which reflects the EPA'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 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, analysts 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 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 EPA 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 EPA 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 the 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 EPA scientists and managers regarding 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.

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 and 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 the 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 the 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, 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 the 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 the 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, 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, 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 analysts 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 analysts 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.

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, 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 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, EPA Region 6 identified the need for a guidance document that consolidated information presented in earlier EPA 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, 2005b), 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 EPA 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 EPA 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, 2001d).

  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 EPA for Toxic Substances and Disease Registry (ATSDR) and reports from the U.S. Geological Survey and universities. EPA 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 EPA Region 6 includes background concentrations in its *Human Health Medium-Specific Screening Levels* document (U.S. EPA, 2005c), 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 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 the 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 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, 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 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.

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).

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 EPA 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 EPA 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 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 the 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 EPA tool for evaluating lead risks (the *All Ages Lead Model*) (U.S. EPA, 2005f) 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 EPA 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 the EPA include *Revised Interim Soil Lead Guidance for CERCLA Sites and RCRA Corrective Action Facilities* (U.S. EPA, 1994a) 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 the 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 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 the 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.). The 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, the 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 analysts 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 analysts 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.

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 EPA's 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.

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 a thorough review process including EPA internal review, expert scientific external review and public review. They represent expert EPA 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 EPA'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, the 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 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 EPA 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 organization and 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 the EPA as hazardous air pollutants 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.

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.

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.

- **Toxicity/Risk Technical Resource (U.S. EPA National Center for Environmental Assessment, NCEA).** As a major research center within the EPA Office of Research and Development (ORD), NCEA serves as the EPA'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 analysts. This organization manages and is responsible for updating the content of the IRIS database (U.S. EPA, 2007). Analysts can contact NCEA for help 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 the 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 the 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. 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, 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 and other EPA documents (e.g., the old Health Effects Assessment Summary Tables (HEAST), which have not been updated since 1997). EPA's Office of Air Quality Planning and Standards has compiled long and short term inhalation and oral toxicity values from several data sources (e.g., values from ATSDR, IRIS and California EPA) that can be found at http://www.epa.gov/ttn/atw/toxsource/summary.html. Information for the MSSLs is presented in technical guidance (U.S. EPA, 2005c) 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 EPA scientists provide guidance and support to analysts across a broad scope of assessment issues, including cumulative health risk.	Serves as a source of single chemical and chemical mixture toxicity assessments and risk assessment methods development.
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.

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 EPA regions, offices, and other organizations. For example, 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.

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 the 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 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 x 10^{-5}), following the 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 the following: 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 EPA Region 6 is GIS-based and looks at multiple sources across the 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 the 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 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 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 EPA website at http://www.epa.gov/osp/presentations/cumrisk/carney.pdf. Region 6 has conducted over 6500 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 noncarcinogens, 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 analysts are 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 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.

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 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 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 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.

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 is expected to show how such toxicity data can be used in conjunction with the toxicity considerations presented in Chapter 4. More detailed chemical-specific information sources are also available (e.g., resources listed in Appendix A). Note that these data on toxicity values are constantly being updated as assessments are revised and created. Users should always check with IRIS and other reliable data sources for current toxicological qualitative evaluations and reference values. Also, note that the tables in this Appendix B focus on noncancer endpoints and may not reflect carcinogenicity or other endpoints of concern for a given chemical.

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 the EPA's IRIS database, current to 2007. 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 quantitative 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 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 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 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 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.

- 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 7-28 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

Example Noncancer Data Table: 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
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	1000
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	1000
Chromium III (insoluble salts) (Cr III)	Liver, spleen	Decreased organ weights	Not established (NOAEL is 1468)	1.5	900
Chromium VI (Cr VI)	No observed effect	No observed effect	Not established (NOAEL is 2.5)	0.003	1000
Dichloroacetic Acid (DCA)	Reproductive system, Developing fetus, Liver, Brain	Lesions in the testes, cerebrum, cerebellum, liver	12.5	0.004	3000
Mercury (based on mercuric chloride) (Hg)	Kidney	Autoimmune glomerulonephritis	0.317	0.0003	1000

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
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	Not established	Not established	Not established
Uranium (soluble salts) (U)	Kidney	Initial body weight loss, moderate nephrotoxicity	2.8	0.003	1000
Zinc (Zn)	Blood	47% decrease in erythrocyte superoxide dismutase concentration (adult females after 10-week exposure)	0.91	0.3	3

[a] Source: U.S. EPA (2007). Note: users should always check with IRIS for current toxicological qualitative evaluations and reference values
[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

Example Noncancer Data Table: 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
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
Nitrite	Not established	No observed effect	Not established	Not established	Not established
Trichloroethylene	Central nervous system, liver and endocrine system	Adverse effects on central nervous system	Not established	Not established	Not established
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 (2007). Note: users should always check with IRIS for current toxicological qualitative evaluations and reference values

[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.

TABLE B-3

Example Noncancer Data Table: 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; (inorganic)	Skin – hyperpigmentation, keratosis; possible vascular complications	U.S. EPA, 2007
	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, 2007 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, 2007 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)

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; (sulfate tetrahydrate)	Multiple target organs; small intestinal lesions.	U.S. EPA, 2007
	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, 2002b)
	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, 2002b)
	Lowest animal LOAEL	12	6000	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, 2002b)

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	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, 2005b (effect type note from RAIS, 1991)
	RfD – food	0.001	1	NOAEL of 0.01 mg/kg-day (food); human study; UF 10	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, 2007 (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 1000	Liver – lesions (mild centrilobular vacuolization and increases in serum sorbitol dehydrogenase activity)	U.S. EPA, 2007
	Lowest human NOAEL	Not reported	NA	NA	NA	NA
	Lowest human LOAEL	Not reported	NA	NA	NA	NA
	Lowest animal NOAEL	1.0	1430	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 1468 mg/kg-day; rat chronic oral study; UF 1000 (chronic oxide)	Liver and spleen – decreased organ weights	U.S. EPA, 2007
	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 1000 (potassium chromate)	No effects	U.S. EPA, 2007
	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 1000; (mercuric chloride)	Kidney – autoimmune glomerulonephritis; assumes the oral absorption of divalent mercury is 7% and absorption from subcutaneous exposure is 100%	U.S. EPA, 2007
	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	Multiple target organs; changes in body and organ weights	U.S. EPA, 2007
	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	Hematopoetic system – methemoglobinemia	U.S. EPA, 2007
	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, 2007)
	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, 2007)
	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, 2007)
	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 10 (from nitrate)	Hematopoetic system – methemoglobinemia	U.S. EPA, 2007
	Lowest human NOAEL	1.0	10	Oral study, infants, nitrate in formula	Hematopoetic system – methemoglobinemia above 10%	Walton, 1951 (cited in U.S. EPA, 2007)
	Lowest human LOAEL	Not reported	NA	NA	NA	NA
Trichloro-ethylene	RfD	NA	NA	NA	Various effects – liver; kidney; developing fetus	ATSDR, 1997c U.S. EPA, 2000i
	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 1000; (30 days) (uranyl nitrate hexahydrate; soluble salt)	Kidney – moderate nephrotoxicity; whole body – initial body weight loss	U.S. EPA, 2007
	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	Hematopoetic system – 47% decreased ESOD conc. (in adult females after 10-week exposure)	Yadrick et al., 1989 (cited in U.S. EPA, 2007)
	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] Note: users should always check with IRIS for current tox qualitative evaluations and reference values. 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., EPA 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 = erythrocyte superoxide dismutase; GI = gastrointestinal system; HDL = high-density lipid; LOAEL = lowest-observed-adverse-effect level; 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.

APPENDIX C
SEVERITY OF TOXIC EFFECT

C.1. OVERVIEW

In 1980, EPA incorporated the judgment of severity of toxic effect into the Ambient Water Quality Criteria (AWQC) methods (U.S. EPA, 1980). Four categories of severity were proposed by EPA as distinguished by the terms:

- No-Observed-Effect Level (NOEL)
- No-Observed-Adverse-Effect Level (NOAEL)
- Lowest-Observed-Adverse-Effect Level (LOAEL)
- Frank-Effect Level (FEL).

EPA (1980) also described the choice of uncertainty factor when a LOAEL was used as the basis of the Acceptable Daily Intake (ADI) (now referred to as the Reference Dose (RfD), where more severe LOAELs yielded larger safety factors (now called uncertainty factors). This judgment also determined whether a LOAEL was really an FEL. If the LOAEL was judged to be an FEL, then an RfD was not estimated because the data base was then judged to not have fully explored the threshold region of toxicity, that is the region where the severity of toxic effect was minimal.

As it was originally envisioned the choice of uncertainty factor (UF) with the use of a LOAEL was to be greater than 1 and up to and including 10, where minimal effects at the LOAEL would be associated with generally a UF of >1 to 5 and more severe or extensive tissue damage at the LOAEL would generally warrant a >5 to 10-fold UF. In practice, however, EPA scientists generally restricted their choices to either 3 or 10 (see U.S. EPA, 2007 for numerous examples). This is because of the difficultly in distinguishing the relative nature of severity within a given organ and among organs, and the corresponding difficulty in being precise with choices of UF.[1]

This early EPA (1980) distinction is evident today, as more fully discussed in Haber et al. (2001) where dose-response processes for noncancer toxicity depend in part on professional judgment as to whether an effect or collection of effects observed

[1] Current discussions of severity often broaden the concept beyond that related to the scientific judgment in the types of endpoints at the LOAEL. This broader concept of severity includes relative judgments of severity among target organs (an exceedingly difficult task), and societal judgments about what is or is not a severe effect and whether or not extra uncertainty factors should be used for certain endpoints. While this broader interpretation is important, the development of noncancer health risk assessment values, such as an RfD, are based on the more limited interpretation and use of the severity concept—as in the 1980 guidelines. While the severity among organ systems is an area of present study and scientific debate, the societal interpretation of severity is best left to the Risk Characterization step of risk assessment/risk management.

at any given dose of a chemical constitutes an adverse response. As before, such judgment may not be easily rendered, and requires experts trained in the area. For example, Figure C-1 taken from Haber et al. (2001) shows individual disability as a function of organ system impairment, and the overlapping areas of adverse and nonadverse effects. Table C-1, also taken from Haber et al. (2001), more clearly describes some of the terms shown in Figure C-1, as well as some other key terms for hazard identification.

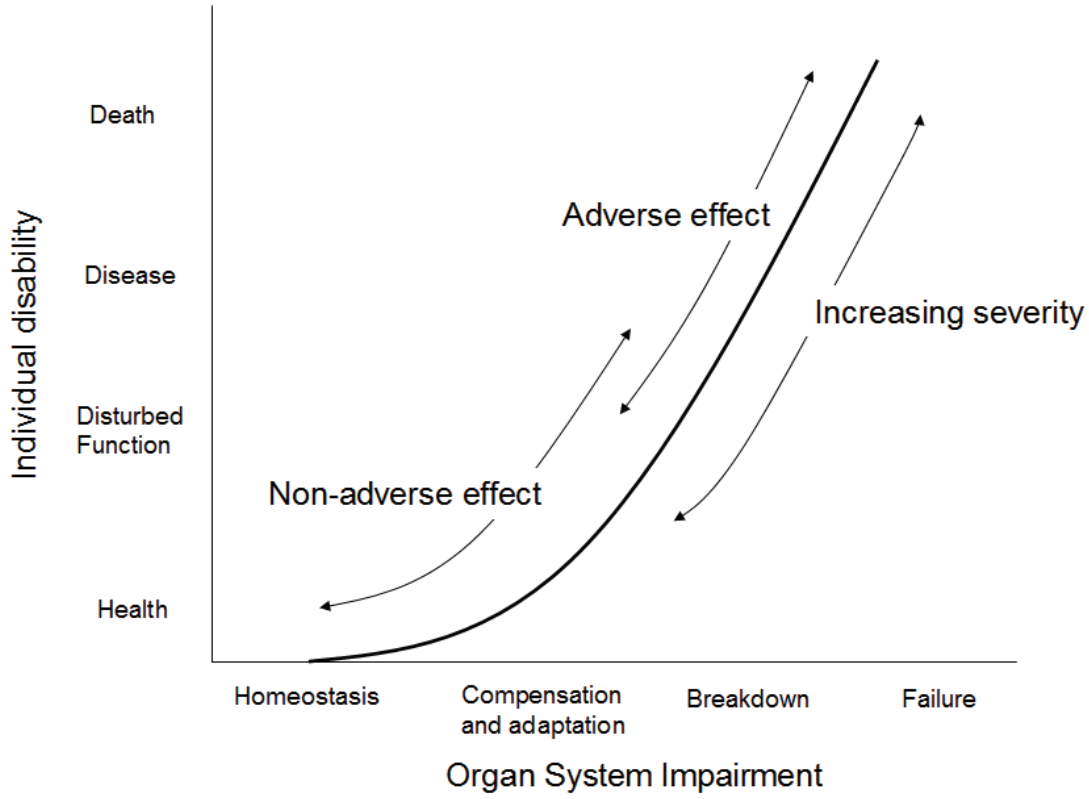
While this figure and table are useful tools to show the broad concept of adversity, the analysis of adversity for a given chemical or situation is strictly a case-by-case analysis by experts. For example, a chemical often elicits more than one toxic effect, even in one species, or in tests of the same or different duration. After assessing the quality of each study, identifying the biological and statistical significance of observed effects (discussed by Haber et al., 2001 and U.S. EPA, 2002e), and distinguishing between reversible and irreversible endpoints (also discussed in Haber et al., 2001), risk assessment scientists often identify the critical effect(s).

The critical effect(s) is the first adverse effect(s) or its known and immediate precursor that occur as dose rate increases in a study. When several studies are compared, the critical effect is generally the lowest one that occurs collectively. Current dose-response methods described in this text and elsewhere use the critical effects as a basis for the dose-response assessment. The critical effects may change among toxicity studies of different durations, may be influenced by toxicity in other organs, and may differ depending on the availability of data on the shape of the dose-response curve.

Where specific guidance on hazard identification is not available, some general considerations regarding the types of toxicity evidence and adversity of effect are needed. Towards this end, risk assessment scientists look at the available data in several different ways, as outlined below. The following considerations illustrate some broad concepts of hazard identification applicable for all organ systems.

C.2. RANKING TOXIC EFFECT

Several schemes are available for ranking the severity of toxic effects. One of the first schemes for noncancer toxicity was developed by EPA scientists in the evaluation of reportable Quantities under the Superfund legislation (DeRosa et al., 1985). These scientists ranked the increasing severity of noncancer health effects as shown in Table C-2.



Adapted from Patty's Toxicology, 2001, Chapter 5

FIGURE C-1
Individual Disability as a Function of Organ System Impairment

TABLE C-1

Some Key Definitions for Hazard Identification

- **ADAPTIVE EFFECT** enhances an organism's performance as a whole and/or its ability to withstand a challenge. An increase in liver weight due to an increase in hepatic smooth endoplasmic reticulum is an example of an adaptive effect, if hepatic metabolism reduces the chemical's toxicity.

- **COMPENSATORY EFFECT** maintains overall function without enhancement or significant cost. Increased respiration due to metabolic acidosis is an example of a compensatory effect.

- **CRITICAL EFFECT** is the first adverse effect, or its known precursor, that occurs as dose rate or exposure level increases. One or more effects may be critical.

- **ADVERSE EFFECT** is a biochemical change, functional impairment, or pathological lesion that impairs performance and reduces the ability of an organism to respond to additional challenge. The determination of such effects may require special tests or observation, such as preparation of slides for histological analysis.

- **FRANK EFFECT** is an unmistakable adverse effect, such as convulsions or mortality. The determination of frank effects can be done by clinical observation and normally does not require special tests.

- **SEVERITY** connotes the toxicological significance attached to the continuum of effects, including adaptive, compensatory, critical, adverse, and frank effects, potentially associated with exposure of xenobiotics.

Source: Haber et al. (2001).

TABLE C-2

Rating Values for NOAELs, LOAELs and FELs Used to Rank Chronic Toxicity

Rating	Effects
1	Enzyme induction or other biochemical change with no pathologic change and no change in organ weights.
2	Enzyme induction and subcellular proliferation or other changes in organelles but no other apparent effects.
3	Hyperplasia, hypertrophy, or atrophy, but no change in organ weights.
4	Hyperplasia, hypertrophy, or atrophy with changes in organ weights.
5	Reversible cellular changes: cloudy swelling, hydropic change, or fatty changes.
6	Necrosis, or metaplasia with no apparent decrement in organ function. Any neuropathy without apparent behavioral, sensory, or physiologic changes.
7	Necrosis, atrophy, hypertrophy, or metaplasia with a detectable decrement in organ functions. Any neuropathy with a measurable change in behavioral, sensory, or physiologic activity.
8	Necrosis, atrophy, or metaplasia with definitive organ dysfunction. Any neuropathy with gross changes in behavior, sensory, or motor performance. Any decrease in reproductive capacity. Any evidence of fetotoxicity.
9	Pronounced pathologic changes with severe organ dysfunction. Any neuropathy with loss of behavioral or motor control or loss of sensory ability. Reproductive dysfunction. Any teratogenic effect with maternal toxicity.
10	Death or pronounced life-shortening. Any teratogenic effect without signs of maternal toxicity.

Source: DeRosa et al. (1985).

Scientists with the ATSDR use a scheme for ranking of severity of toxic effect that is intermediate between the EPA (1980) version and the one used for Reportable Quantities (DeRosa et al., 1985). This scheme by ATSDR (Pohl and Abadin, 1995) has the following 5 severity rankings:

- No-Observed-Effect Level (NOEL)
- No-Observed-Adverse-Effect Level (NOAEL)
- Minimal-Lowest-Observed-Adverse-Effect Level ($LOAEL_1$)
- Moderate-Lowest-Observed-Adverse-Effect Level ($LOAEL_2$)
- Frank-Effect Level (FEL).

In addition, it is still the current practice to use a varying uncertainty factor with a LOAEL used to estimate an RfD/RfC. The choice of uncertainty factor to be extrapolated to the NOAEL generally depends on the severity of the effect at the LOAEL. Sometimes this uncertainty factor is used with the choice of a benchmark dose (BMD) of moderate severity, although this latter use is not uniform nor universally accepted. In either case, more severe effects should be judged to need a larger uncertainty factor because the expected NOAEL is further away from the LOAEL or BMD. Less severe effects would not require a large factor, because, presumably, the LOAEL or BMD is closer to the unknown NOAEL (Dourson et al., 1996).

For cancer toxicity, it is recognized that tumors vary in severity, with the most common distinction made between malignant and benign categories. However, these distinctions in severity do not generally affect the quantitative dose response assessment, other than to categorize the evidence that a chemical causes the cancer endpoint or not. Older categories of cancer evidence from EPA (1986b) are:

- Group A: Known human carcinogen. Substances for which "sufficient" evidence from human epidemiologic studies supports a causal connection between exposure to the substance and cancer.
- Group B1: Probable human carcinogen (limited human evidence). Weight of evidence of human carcinogenicity based on epidemiologic studies is "limited."
- Group B2: Probable human carcinogen (no human evidence). Substances for which there is "no data," or "no evidence" from human epidemiologic studies, but for which the weight of evidence of carcinogenicity based on animal studies is "sufficient."
- Group C: Possible human carcinogen. Substances with "limited" evidence of carcinogenicity in animals, and "inadequate evidence," "no data" or "no evidence" from human epidemiologic studies.
- Group D: Not evaluated. Not classifiable for human carcinogenicity (insufficient data).
- Group E: Noncarcinogenic. Evidence of noncarcinogenicity in humans (U.S. EPA, 1986b).

EPA's newer classification (U.S. EPA, 2005d) also emphasizes categories of cancer evidence, rather than severity of endpoint. These categories are:

- Carcinogenic to humans
- Likely to be carcinogenic to humans
- Suggestive evidence of carcinogenic potential
- Inadequate information to assess carcinogenic potential
- Not likely to be carcinogenic to humans.

As with the early guidelines of 1986 these categorizations do not make distinctions of severity, and thus severity does not generally affect the quantitative dose response assessment.

C.3. EXAMPLES OF SEVERITY USE FOR QUANTITATIVE DOSE RESPONSE ASSESSMENT

Work by EPA over a number of years indicates that the regression of toxicity data viewed as categories of pathological staging is useful for exploring the likely health risk at doses above the RfD/RfC. This categorical regression has both theoretical support by Hertzberg and colleagues and practical application for individual chemicals (e.g., Hertzberg and Miller, 1985; Hertzberg and Wymer, 1991). For example, Dourson et al. (1997) used categorical regression for developing risks above the RfD for aldicarb. In this paper the severity of cholinergic effects was described using the EPA (1980) breakdown of severity:

- Frank effects (FEL): Abdominal pain, nausea and/or vomiting, diarrhea, seizures, disorientation or confusion, excitation, or mortality
- Adverse effects (LOAEL): Brain, whole blood or RBC cholinesterase inhibition of more than 20%, muscular weakness or twitching, blurred vision and/or watery eyes, pinpoint pupils, excess salivation, sweating or clamminess, hyperactivity or altered patterns of locomotion
- Non-adverse effects (NOAEL): Whole blood, RBC or plasma cholinesterase inhibition of less than 20%
- No effects (NOEL).

Teuschler et al. (1999) also expanded the use of categorical regressions to compare the likely risks at exposures above the RfDs for multiple chemicals with different critical effects. Existing health risk data for diazinon, disulfoton, EPTC, fenamiphos and lindane were analyzed. As expected, the estimated risks of adverse effects above the RfD varied among the chemicals. For example, at 10-fold above the RfD these risks were modeled to be 0.002, 0.0001, 0.0007, 0.002, 0.02, respectively. The results and impacts of this analysis further indicate that categorical regression is a useful screening tool to analyze risks above the RfD for specific chemicals, and suggest

its application in evaluating comparative risks where multiple chemical exposures exist. Not surprisingly, categorical regression has been cited in a number of methods texts since these publications and is actively used in a number of situations, including air toxics evaluations (e.g., Elder et al., 2002; Guth et al., 1997).