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Framework for Cumulative Risk Assessment

RISK ASSESSMENT FORUM

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Framework for Cumulative Risk Assessment

Risk Assessment Forum
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Table of Contents

List of Figures

List of Text Boxes

Acknowledgments

This U.S. Environmental Protection Agency (EPA or the Agency) report has been developed under the auspices of EPA's Risk Assessment Forum, a standing committee of EPA scientists charged with developing risk assessment guidance for Agency-wide use. An interoffice Technical Panel chaired by Michael A. Callahan (Region 6) was commissioned to write this report. Other members of the Panel are Edward S. Bender (Office of Science Policy), George L. Bollweg (Region 5), Vicki L. Dellarco (Office of Pesticide Programs), Lynn A. Delpire (Office of Pollution Prevention and Toxics), Martin P. Halper (Office of Environmental Justice), Richard C. Hertzberg (National Center for Environmental Assessment), Elizabeth Lee Hofmann (Office of Emergency and Remedial Response), R. Craig Matthiessen (Chemical Emergency Preparedness and Prevention Staff), Alexander McBride (Office of Solid Waste), Deirdre L. Murphy (Office of Air Quality Planning and Standards), Henry C. Topper (Office of Pollution Prevention and Toxics), and Winona Victery (Region 9).

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Foreword

Several reports have highlighted the importance of understanding the accumulation of risks from multiple environmental stressors. Among these reports are the National Research Council's 1994 *Science and Judgment in Risk Assessment* and the 1997 report by the Presidential/Congressional Commission on Risk Assessment and Risk Management, *Risk Assessment and Risk Management in Regulatory Decision-Making*. In addition, legislation such as the Food Quality Protection Act of 1996 (FQPA), has directed the U.S. Environmental Protection Agency (EPA, or the Agency) to move beyond single chemical assessments and to focus, in part, on the cumulative effects of chemical exposures occurring simultaneously. Some of the cases filed with EPA under Title VI of the 1964 Civil Rights Act further emphasize the need for EPA to develop methods to assist consideration of cumulative risks.

The Superfund program began conducting cumulative risk assessments at hazardous waste sites as early as the 1980s. More recently, in response to the increasing interest in cumulative risk, several other EPA programs have begun to explore approaches to cumulative risk assessment. In 1997, the EPA Science Policy Council issued a guidance on planning and scoping for cumulative risk assessments. More recently, the Office of Pesticide Programs has developed cumulative risk assessment guidance focused on implementing certain provisions of FQPA. In addition, the Office of Air Quality Planning and Standards is performing a national-scale cumulative assessment of human health risks posed by outdoor air exposures to a set of 33 priority urban air toxics.

The EPA Science Policy Council has asked the Risk Assessment Forum to begin developing Agency-wide cumulative risk assessment guidance that builds from these ongoing activities. As a first step, a technical panel convened under the Risk Assessment Forum has been working to develop a framework for cumulative risk assessment. This document is the result of that technical panel's efforts. Building from the Agency's growing experiences, this framework is intended to identify the basic elements of the cumulative risk assessment process. It should provide a flexible structure for the technical issues and define key terms associated with cumulative risk assessment. Further efforts and experience in the coming years should advance our knowledge beyond the framework stage to a future set of Agency guidelines for cumulative risk assessment.

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Preface

In the past several years, cumulative risk assessment, aggregate exposure assessment, and research on chemical mixtures has taken on increased importance, as evidenced by reports such as the National Research Council's (NRC's) *Pesticides in the Diets of Infants and Children* (NRC, 1993) and *Science and Judgment in Risk Assessment* (NRC, 1994), the National Academy of Public Administration's *Setting Priorities, Getting Results* (NAPA, 1995), the Presidential/Congressional Commission on Risk Assessment and Risk Management's *Risk Assessment and Risk Management in Regulatory Decision-Making* (PCCRARM, 1997), and the U.S. Environmental Protection Agency's (EPA's or the Agency's) Science Advisory Board *Toward Integrated Environmental Decision-Making* (USEPA, 2000a).

In addition, recent legislation mandates consideration of cumulative risk and variability factors in the risk characterization process. Specifically, the Food Quality Protection Act of 1996 (FQPA) (PL 104-170, August 3, 1996) directs EPA in its assessments of pesticide safety to focus, in part, on the cumulative effects of pesticides that have a common mechanism of toxicity, considering aggregate dietary and nonoccupational pathways of exposure.

Assessing cumulative risk through complex exposures is one of the Agency's high priorities, especially in light of FQPA mandates, and it is germane and of great interest to all program and regional offices. This area of research is also directly applicable to children's risk issues. The framework presented in this document is meant to lay out broad areas where analysis might be conducted if needed. It is not suggested that cumulative risk assessment is a tool that should be used with every issue or that all areas of analysis outlined or discussed here must—or even should be—conducted in every such assessment. The scope of the assessment will define the areas to be analyzed. For some areas discussed in this framework, the methodology for conducting the risk analysis may not yet exist.

According to an expert panel report (USEPA, 1992a), a key role of science at EPA is to reduce uncertainties in the information used for environmental decision making. The report points out that although many EPA programs have historically focused on chemical-specific impacts, methods to assess or control the effects of chemical mixtures and general stressors on human health and ecosystems remained to be developed.

NRC (1993) has recommended that all exposures to pesticides—dietary and nondietary—need to be considered when evaluating the potential risks to infants and children. Estimates of total dietary exposure should be refined to consider intake of multiple pesticides that have a common toxic effect. Further, the report identifies important differences in susceptibility with age. NRC (1994) has also stated that health risk assessments should generally consider all possible routes by which people at risk might be exposed and recommends this approach universally in the assessment of hazardous air pollutants regulated by EPA under the Clean Air Act Amendments of 1990 (P.L. 101-549, November 15, 1990).

Regarding variability, the NRC (1994) recommends that EPA assess risks to infants and children whenever it appears that their risks might be greater than those of adults. The report also encourages EPA to recognize the possibility of synergistic interactions when multiple chemical exposures occur, and to consider extreme variability among individuals in their responses to toxic substances. A related issue is the problem of how risks associated with multiple chemicals are to be combined. EPA hopes to begin systematically addressing these issues in this framework.

Finally, FQPA requires research on the influence of complex exposures on noncancer human health effects of pesticides and other toxic substances.

Cumulative risk is also an important issue with the general public. In public meetings of Superfund stakeholders held in late 1996 in San Francisco and Washington, DC, and in early 1998 in Atlanta, the issue of cumulative risk was raised several times in each session (USEPA, 1996a, 1998a).

Cumulative risk assessments will identify the need for many different kinds of data—some of which are not commonly used in current risk assessment—and they will often demand large quantities of such data. Until such data can be provided, identification of critical information and research needs may be the primary result of many cumulative risk assessment endeavors.

As of August 1, 2001, there were 19,533 pesticide products on the market (USEPA, 2001a) and 79,120 existing chemicals on the Toxic Substances Control Act inventory (USEPA, 2001b). Each year, a number of chemicals are added. Assessing the cumulative effect of these chemicals will be a great challenge to to the field of risk assessment and to the Agency.

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List of Abbreviations and Acronyms

APEX	- Air Pollution EXposure model
ATSDR	- Agency for Toxic Substances and Disease Registry
CARES	- Cumulative and Aggregate Risk Evaluation System
CBEP	- Community-Based Environmental Protection
DALY	- Disability-Adjusted Life Year
EPA	- U.S. Environmental Protection Agency
FQPA	- Food Quality Protection Act
GIS	- Geographical Information System
HAP	- Hazardous Air Pollutant
HEC	- Human Equivalent Concentration
HRS	- Hazard Ranking System
HUD	- U.S. Department of Housing and Urban Development
IED	- Integrated Environmental Decision-making
ILSI	- International Life Sciences Institute
LADD	- Lifetime Average Daily Dose
LLE	- Loss of Life Expectancy
LOAEL	- Lowest-Observed-Adverse-Effect Level
MSDS	- Materials Safety Data Sheet
NAAQS	- National Ambient Air Quality Standards
NATA	- National Air Toxics Assessment
NEPA	- National Environmental Policy Act
NHEXAS	- National Human Exposure Assessment Survey
NOAEL	- No-Observed-Adverse-Effect Level
NRC	- National Research Council
OAR	- Office of Air and Radiation (EPA)
OP	- Organophosphorous
OPP	- Office of Pesticide Programs (EPA)
OPPTS	- Office of Prevention, Pesticides, and Toxic Substances (EPA)
ORD	- Office of Research and Development (EPA)
PAH	- Polycyclic Aromatic Hydrocarbon
PCB	- Polychlorinated Biphenyl
pNEM	- Probabilistic NAAQS Exposure Model
QALY	- Quality-Adjusted Life Year
RfC	- Reference Concentration
RfD	- Reference Dose
SAB	- Science Advisory Board
SHEDS	- Stochastic Human Exposure and Dose Simulation model
TEAM	- Total Exposure Assessment Methodology
TEF	- Toxicity Equivalence Factor

Executive Summary

This report, *Framework for Cumulative Risk Assessment*, is the first step in a long-term effort to develop cumulative risk assessment guidelines. Its primary purpose is to offer a simple, flexible structure for conducting and evaluating cumulative risk assessment within the U.S. Environmental Protection Agency (EPA, or the Agency). Although this framework report will serve as a foundation for developing future guidelines, it is neither a procedural guide nor a regulatory requirement within EPA, and it is expected to evolve with experience. This report is intended to foster consistent approaches to cumulative risk assessment within EPA, identify key issues, and define terms used in these assessments.

This framework is meant to lay out broad areas where analysis might be conducted if needed. It does not suggest that cumulative risk assessment is a tool that should be used with every issue, nor does it suggest that when cumulative risk assessment is applied, that all areas of analysis outlined or discussed here must—or even should be—conducted in every assessment. The scope of the assessment will define the areas to be analyzed. In some areas discussed in this framework, the methodology for doing the risk analysis may not yet exist. Appendix A includes a summary of areas where research is needed.

In this report, "cumulative risk" means "the combined risks from aggregate exposures to multiple agents or stressors." Several key points can be derived from this definition of cumulative risk. First, cumulative risk involves multiple agents or stressors, which means that assessments involving a single chemical or stressor are not "cumulative risk assessments" under this definition. Second, there is no limitation that the "agents or stressors" be only chemicals; they may be, but they may also be biological or physical agents or an activity that, directly or indirectly, alters or causes the loss of a necessity such as habitat. Third, this definition requires that the risks from multiple agents or stressors be combined. This does not necessarily mean that the risks should be "added," but rather that some analysis should be conducted to determine how the risks from the various agents or stressors interact. It also means that an assessment that covers a number of chemicals or other stressors but that merely lists each chemical with a corresponding risk without consideration of the other chemicals present is not an assessment of cumulative risk under this definition.

"Cumulative risk assessment" in this report means "an analysis, characterization, and possible quantification of the combined risks to health or the environment from multiple agents or stressors." One key aspect of this definition is that a cumulative risk assessment need not necessarily be quantitative, so long as it meets the other requirements.

The framework itself is conceptually similar to the approach used in both human health and ecological assessments, but it is distinctive in several areas. First, its focus on the combined effects of more than one agent or stressor makes it different from many assessments conducted today, in which, if multiple stressors are evaluated, they are usually evaluated individually and presented as if the others were not present. Second, because multiple stressors are affecting the same population, there is increased focus on the specific populations potentially affected rather

than on hypothetical receptors. Third, consideration of cumulative risk may generate interest in a wider variety of nonchemical stressors than do traditional risk assessments.

The framework describes three main phases to a cumulative risk assessment: (1) planning, scoping, and problem formulation, (2) analysis, and (3) risk characterization. In the first phase, a team of risk managers, risk assessors, and other stakeholders establishes the goals, breadth, depth, and focus of the assessment. The end products of this phase are a conceptual model and an analysis plan. The conceptual model establishes the stressors to be evaluated, the health or environmental effects to be evaluated, and the relationships among various stressor exposures and potential effects. The analysis plan lays out the data needed, the approach to be taken, and the types of results expected during the analysis phase.

The analysis phase includes developing profiles of exposure, considering interactions (if any) among stressors, and predicting risks to the population or populations assessed. It is in this phase that difficult technical issues such as the toxicity of mixtures, the vulnerability of populations, or the interactions among stressors that may be chemical or nonchemical are addressed and, hopefully resolved. The end product of this phase is an analysis of the risks associated with the multiple stressors to which the study population or populations are exposed.

The third phase, risk characterization (interpretation), puts the risk estimates into perspective in terms of their significance, the reliability of the estimates, and the overall confidence in the assessment. It is also in this phase that an evaluation is made of whether the assessment met the objectives and goals set forth in phase one.

The discussion of cumulative risk in this framework report takes a broad view of the topic and includes many aspects of an assessment that might conceivably be conducted in the future, even though techniques may not currently exist to examine every question. It also includes aspects of cumulative risk that may be outside of EPA's current legislative mandates and where expertise outside of the Agency would be needed to address certain questions if they should arise. These aspects are discussed here for the sake of technical completeness and not as a recommendation that EPA perform all possible aspects of a cumulative risk assessment in all its risk assessments—even all its cumulative risk assessments. This framework may, however, provide an opportunity for the Agency to start to integrate the requirements of its various legislative mandates, at least in the area of risk assessment.

EPA is currently engaged in activities that fall under various aspects of the cumulative risk assessment umbrella. Some of these activities are listed as illustrations in the box on the next page. The broad interpretation of cumulative risk in this framework report allows these activities to be put into perspective relative to one another and can illustrate how the activities fit together under the framework. Individual Program Offices and Regions may have to make decisions that affect the scope, types of stressors, or methods used for their programs' cumulative risk assessments, based on legislative mandates or other criteria. Nothing in this

Examples of Cumulative Risk Assessment Activities within EPA in 2002

- The **Superfund Program** has updated its guidance on risk assessment to include planning and scoping for cumulative risk assessment and problem formulation for ecological risk assessments. The plan for the **Office of Solid Waste's** Surface Impoundment Study includes both a conceptual model and an analytical plan, per the agency guidance on planning and scoping for cumulative risk.

- The **Office of Water** is planning a watershed-scale risk assessment involving multiple stressors in ecological risk. This approach was developed through a collaboration with external scientists and is now being field evaluated.

- Several **Regional Offices** are evaluating cumulative hazards, exposures, and effects of toxic contaminants in urban environments. In Chicago (**Region 5**), citizens are concerned about the contribution of environmental stressors to endpoints such as asthma and blood lead levels. In Baltimore (**Region 3**), a regional/**Office of Prevention, Pesticides, and Toxic Substances**/community partnership tried to address the long-term environmental and economic concerns in three neighborhoods that are adjacent to industrial facilities and tank farms. **Region 6** (Dallas) is developing a geographic information system approach for planning and scoping cumulative risks.

- The Food Quality Protection Act of 1996 requires that EPA consider the cumulative effects to human health that can result from exposure to pesticides and other substances that have a common mechanism of toxicity. The **Office of Pesticide Programs** has developed guidance for conducting cumulative risk assessments for pesticides and has prepared a preliminary cumulative risk assessment for organophosphorous pesticides.

- The **Office of Air and Radiation's (OAR's)** air toxics program has a cumulative risk focus. Under the Integrated Urban Air Toxics Strategy, OAR will be considering cumulative risks presented by exposures to air emissions of hazardous air pollutants from sources in the aggregate. Assessments will be performed at both the national scale (a national-scale assessment for base year 1996 was completed in 2002) and at the urban or neighborhood scale. In partnership with the **Office of Research and Development** (ORD) and the **National Exposure Research Laboratory**, the **Office of Air Quality Planning and Standards** is developing the Total Risk Integrated Methodology (TRIM), a modular, modeling system for use in single or multimedia, single or multipathway human health and ecological risk assessments of hazardous and criteria air pollutants at the neighborhood or city scale. The Agency's guidance for planning and scoping cumulative risk was used to develop a conceptual model and analysis plan for the national-scale air toxics risk assessment.

- ORD's **National Center for Environmental Assessment** (NCEA) has completed ecological risk assessment guidelines that support the cumulative risk assessment guidance. Five watershed case studies are being assessed to demonstrate the guidelines approach. Each of these cases deals with cumulative impacts of stressors (chemical, biological, and, in some cases, physical). In addition, NCEA has prepared a draft reassessment of dioxin and related compounds.

- The **Risk Assessment Forum** convened a technical panel to develop guidance for conducting cumulative risk assessments, of which this framework is a first step.

report should be interpreted as mandating that a cumulative risk assessment be conducted or be conducted in a certain way for any specific case. Likewise, this report is not an attempt to lay out protocols to address all the risks or considerations that are needed to adequately inform community decisions. Rather, it is an information document, focused on describing various aspects of cumulative risk *whether or not the methods or data currently exist to adequately analyze or evaluate those aspects of the assessment.* Because of the limitations of current science, cumulative risk assessments done in the near future will not be able to adequately answer all the questions posed by stakeholders or interested parties. This does not mean, however, that they cannot answer *some* of the questions; in fact, cumulative risk assessment may be the best tool available to address certain questions dealing with multiple-stressor impacts.

1. INTRODUCTION

During much of its early history, the U.S. Environmental Protection Agency (EPA, or the Agency) focused its efforts on cleaning up the overt pollution problems of the 1960s and 1970s. Until the Agency was established, in 1970, relatively uncontrolled air emissions, water effluents, and dumped wastes had led to pollution of the environment that was easily detected by the five senses. The most effective and efficient way of approaching these overt problems of the 1970s was to find the entry point of the pollutant into the environment and to control it at that point. Looking back, we see a strategy that moved to control stack emissions, industrial and municipal effluents, pesticide application, land applications, burial of chemical wastes, and other "sources" of pollution. In addition, criteria and standards were established as goals for cleaning up the various environmental media. By the 1980s, this "command and control" strategy was well established in environmental laws and regulations but was reaching the point of diminishing returns from a cost-benefit viewpoint.

The development of risk assessment methodology during the 1970s and early 1980s closely followed the Agency's strategy for control of pollution, because risk assessments were being used as a factor in EPA's regulatory decision making. The focus on sources led naturally to analyses of what types of pollutants were in effluents, air emissions, and waste sites and the detection of chemical, biological, and—sometimes—radiological agents. By the 1970s, the link between some chemicals and certain diseases such as cancer had been established through a series of bioassays or, in the case of chemicals such as vinyl chloride and asbestos, through epidemiological studies. New analytical techniques also made it possible for the first time to detect very minute concentrations of chemicals. The focus of the EPA strategy to control pollution (and the risk assessment methodology being used to partially support decisions) gradually leaned toward assessing and controlling the individual chemicals. Congressional legislation tended to underwrite this approach by focusing on controlling sources and even including lists of individual chemicals to be controlled.

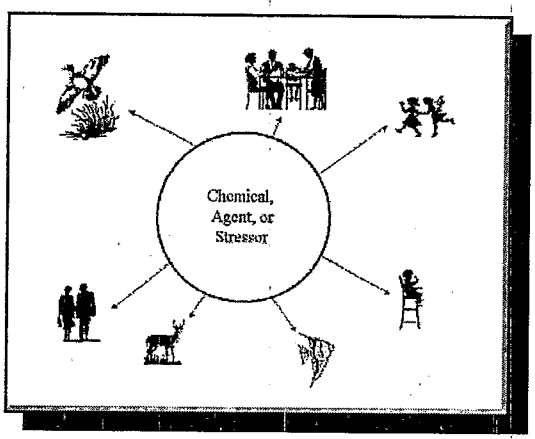

Figure 1-1. A chemical- (or stressor-) focused assessment starts with a source and evaluates how the chemical gets to various populations or ecological targets. Individual assessments may pursue some or all pathways, media, or population segments.

The risk assessment methodology of the 1970s and early 1980s, therefore, tended toward single-chemical assessments (Figure 1-1). A National Research Council (NRC) report (NRC, 1983) was focused largely on the single-chemical risk assessment approach when it spoke of the four parts of a Federal risk assessment: hazard identification, dose-response assessment,

exposure assessment, and risk characterization. EPA's 1986 risk assessment guidelines (USEPA, 1986a), with the exception of the mixtures guidelines (USEPA, 1986b), also focused largely on single-chemical assessment.

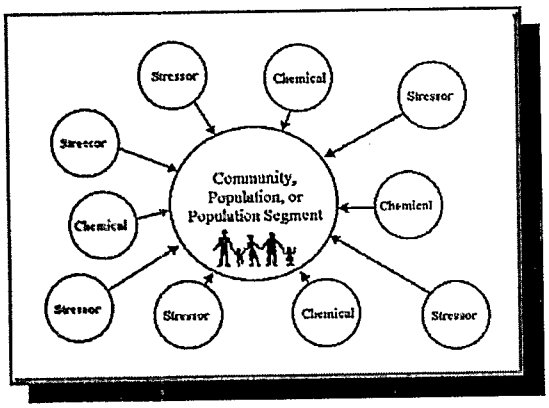

Figure 1-2. Population-based assessments start with the receptors and determine which chemicals, stressors, or other risk factors are affecting them.

However, research conducted or sponsored by EPA in the early 1980s was taking the first steps toward investigating a different type of risk assessment methodology, one that focused on identifying the persons exposed, investigating the chemicals or stressors to which they were exposed, and determining consequent risks (Figure 1-2). This approach differs from those that focus on either a chemical (and investigates the chemical environmental fate, exposed populations, and risks [Figure 1-1]) or a source (and investigates environmental releases from that source, exposed populations, and risks). The goals of the population-focused approach[1] were much more useful to decisionmakers who were dealing with public health or ecological health questions rather than controlling sources of pollution.

The challenges posed by the population-based assessment can be daunting, even if only a few of the stressors affecting a population are evaluated together (i.e., cumulatively). Taken to the extreme, Figure 1-2 represents a concept of "total risk" for the population or population segment being evaluated, with each chemical, biological, radiological, or other stressor[2] adding some fraction of the total risk. Looking at the problem from an individual stressor viewpoint, to do this type of assessment would require not only evaluating each individual stressor, but also developing a way to add up all the risks among stressors across a population of individuals with

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[1] A chemical-focused assessment may look at several populations affected by exposure to the chemical but not at other chemicals. A population-focused assessment looks at one population for perhaps many stressors but not at other populations. Consequently, for traditional, chemical-focused assessments, we say we conduct a "risk assessments for a certain chemical." In contrast, the essence of a cumulative risk assessment is that the assessment is conducted "for a certain population." This difference is shown schematically by comparing Figures 1-1 and 1-2. How the population is identified for a cumulative assessment is not addressed here.

[2] A stressor is a physical, chemical, biological, or other entity that can cause an adverse response in a human or other organism or ecosystem. Exposure to a chemical, biological, or physical agent (e.g., radon) can be a stressor, as can the lack of, or destruction of, some necessity, such as a habitat. The stressor may not cause harm directly, but it may make the target more vulnerable to harm by other stressors. A socioeconomic stressor, for example, might be the lack of needed health care, which could lead to adverse effects. Harmful events, such as automobile crashes, could also be termed stressors. Obviously, calculating risks from different types of stressors can use widely differing methods, including probabilistic estimates of disease via dose-response relationships or looking up rates in statistical tables of historical events, among others.

different exposures and susceptibilities. In the early 1980s, the state of the science was unready for virtually any part of the methods for doing this type of assessment.

But progress was being made toward developing a population-based methodology. Starting in the late 1970s, a group of EPA researchers and contractors began developing what would become the Total Exposure Assessment Methodology (TEAM) study (USEPA, 1987). TEAM measured the concentrations of a number of chemicals simultaneously at the point of exposure. This project led to a larger study, the National Human Exposure Assessment Survey (NHEXAS) in the 1990s (Sexton et al., 1995). Both TEAM and NHEXAS developed analytical tools and methodologies to do population-based exposure assessments.

Some progress was also being made in the early 1980s on the question of how to cumulatively consider the risks from different chemicals or stressors. EPA's 1986 risk assessment guidelines (USEPA, 1986a) included a guideline on chemical mixtures (USEPA, 1986b), which discussed how the risks from multiple chemicals could be evaluated as a whole. Work on this guidance has continued most recently with *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (USEPA, 2000e), which expands and supplements the 1986 effort.

As progress was being made on single chemical and chemical mixture risk assessment with the 1986 guidelines, some different kinds of risk assessment problems began to catch the Agency's attention. In 1986, 11 Chicago-area community groups joined to file a petition under Section 21 of the Toxic Substances Control Act, asking for a community assessment in Southeast Chicago. A series of community-based actions that started in 1982 and grew throughout the 1980s focused on disparities of risk among various population subgroups, calling specific attention to cumulative effects of pollution on minority subgroups (GAO, 1983; United Church of Christ, 1987). This series of community-based actions, chronicled by Bullard (1990), eventually became known as the movement. The issues raised by the movement were the basis of a 1994 Presidential Executive Order (Executive Order 12898, February 11, 1994), which told federal agencies, among other things, to consider multiple and cumulative exposures whenever practicable and appropriate. In the 1990s, Environmental Justice cases, including the cases filed under Title VI of the 1964 Civil Rights Act, [P.L. 88-352, July 2, 1964] have further emphasized the need for a cumulative human health risk assessment methodology.

It was apparent that in addition to chemical- or stressor-focused assessments (as shown in Figure 1-1), population-focused assessments (as shown in Figure 1-2) would be needed if EPA was going to be able to answer the questions and issues being raised by the public. Community spokespersons and other stakeholders, as well as scientific panels, were increasingly coming to the Agency with problems that demanded a multi-stressor approach (e.g., NRC 1994). Ecological problems in particular were demanding a "place-based" context (such as the Chesapeake Bay watershed) in which the various populations within the area were looked at from a "total system" viewpoint. This place-based focus was part of *Framework*

for Ecological Risk Assessment (USEPA, 1992b) and *Guidelines for Ecological Risk Assessment* (USEPA, 1998b).

Although clearly addressing more than cumulative human health or ecological risk assessment, the National Environmental Policy Act of 1969 (NEPA) (P.L. 91-190, 42 U.S.C. 4321-4347, January 1, 1970, as amended by P.L. 94-52, July 3, 1975, P.L. 94-83, August 9, 1975, and P.L. 97-258, §4(b), Sept. 13, 1982), which was passed at about the same time EPA was established, requires assessments on the cumulative impacts of federal or federally funded projects (such as roads, dams, power lines, military projects, and infrastructure development) on natural ecosystems, endangered species, habitats, and opportunities for public enjoyment and natural resource use. A primary concern for NEPA is "cumulative effects analysis," defined as "the incremental impact of the action when added to other past, present, and reasonably foreseeable future actions. . . . Cumulative impacts result from individually minor but collectively significant actions taking place over a period of time" (CEQ, 1997). Much of the NEPA cumulative effects analysis is qualitative, but risk assessments and cause-and-effect relationships are key parts of the analysis process for controversial projects.

In 1997, the Agency issued a policy memo, *Guidance on Cumulative Risk Assessment, Part 1: Planning and Scoping* (USEPA, 1997a), which took the first formal step toward developing guidance and guidelines for cumulative risk assessment.

Cumulative risk assessment applications have become relatively common, not only for assessments of chemicals that operate by the same mode of action, as mandated for the EPA's pesticides program, but also for community-based, population-based, assessments that may include more varied stressors than just chemicals alone. Much like the "place-based" ecological assessments, which may cover a wide variety of physical, chemical, and biological stressors, some communities have added human health and perhaps "quality of life" to the endpoints of interest in their place-based assessments. The demand for more sophisticated human health risk assessments has driven the need for research into cumulative risk assessment, population-focused assessments, aggregate exposure assessment, and risk from chemical mixtures.

1.1. Purpose and Scope of the Framework Report

An understanding of the finite purpose and scope of this framework report is important. EPA and other organizations need detailed, comprehensive guidance on methods for evaluating cumulative risk. Before such detailed Agency-level guidance is developed on a relatively new field of risk assessment, it has been the recent policy of the Agency to first develop a simple framework as a foundation for later comprehensive guidance. This *Framework for Cumulative Risk Assessment* emphasizes chemical risks to human health in its discussion and also in the context of the effects from a variety of stressors, including nonchemical stressors. Some important topics that could be characterized as "cumulative risk," such as global climate change, are beyond the scope of this report.

Given this background, the framework has two simple purposes, one immediate and one longer term. As a broad outline of the assessment process, the framework immediately offers a basic structure and provides starting principles for EPA's cumulative risk assessments. The process described by the report provides wide latitude for planning and conducting cumulative risk assessments in many diverse situations, each based on common principles discussed in the report. The process also will help foster a consistent EPA approach for conducting and evaluating cumulative risk assessments, for identifying key issues, and for providing operational definitions for terms used in cumulative risk assessments.

In the longer term, the framework report offers the basic principles around which to organize a more definitive set of cumulative risk assessment guidance. With this in mind, this report does not provide substantive guidance on certain issues that are integral to the risk assessment process (see box on this page and Appendix B for a listing of useful resources). These issues include specific analytical methods, techniques for analyzing and interpreting data, and guidance on issues influencing policy. Rather, on the basis of EPA experience and the recommendations of peer reviewers, EPA has reserved discussion of these important aspects of cumulative risk assessment for future guidance, which will be based on the risk assessment process described in this framework report.

EPA's Risk Assessment Guidelines

Chemical mixtures (USEPA, 1986b)
Mutagenicity risk assessment (USEPA, 1986c)
Carcinogen risk assessment (USEPA, 1986d)
Developmental toxicity risk assessment (USEPA, 1991a)
Exposure assessment (USEPA, 1992c)
Reproductive toxicity risk assessment (USEPA, 1996b)
Proposed carcinogen risk assessment (USEPA, 1996c, 1999a, b)
Ecological risk assessment (USEPA, 1998b)
Neurotoxicity risk assessment (USEPA, 1998c)

Selected Policy and Guidance Documents

Risk assessment guidance for superfund (USEPA, 1989a)
Locational data policy (USEPA, 1991b)
Framework for ecological risk assessment (USEPA, 1992b)
Application of refined dispersion models (USEPA, 1993a)
Policy/guidance for risk characterization (USEPA, 1995a, b)
Benchmark dose (USEPA, 1995c, 2000b)
Cumulative risk planning and scoping (USEPA, 1997a)
Guiding principles for Monte Carlo analysis (USEPA, 1997b)
Acute inhalation exposure (USEPA, 1998d)
Chemical emergency risk management (USEPA, 1998e)
Draft comparative risk framework (USEPA, 1998f)
Aggregate exposure and risk (USEPA, 1999g)
Community involvement in Superfund risk assessment (USEPA, 1999c)
Guidance for offsite consequence analysis (USEPA, 1999d)
Guideline on air quality models (USEPA, 1999e)
Framework for community-based environmental protection (USEPA, 1999f)
Handbook for risk characterization (USEPA, 2000c)
Handbook for peer review (USEPA, 2000d)
Supplementary guidance for conducting health risk assessment of chemical mixtures (USEPA, 2000e)
Cumulative risk assessment of pesticide . . . common mechanism of toxicity (USEPA, 2002a)

This report lays out broad areas where analysis might be conducted if needed. It does not suggest that cumulative risk assessment is a tool that should be used with every issue, nor does it suggest that when cumulative risk assessment is applied, all areas of analysis outlined or

discussed here must or even should be conducted in every assessment. The scope of the assessment should be defined in the planning and scoping stage (see Section 2.1) and may include or exclude stressors or pathways as relevant to the particular context or application. In some areas discussed in this report, the methodology for doing the risk analysis may not yet exist.

Following completion of this framework report, EPA plans to initiate development of a more detailed guidance document. As a first step in this process, EPA will oversee the preparation of a number of case studies and issue papers on select topics. In addition, the Agency plans to hold workshops to further evaluate those issues. Following these activities, EPA will begin drafting the more detailed guidance in the form of *Guidelines for Cumulative Risk Assessment.* At this time, the Agency does not have a definite schedule for these activities.

1.2. Intended Audience

This framework report is primarily intended for EPA risk assessors, EPA risk managers, and other persons who either perform work under EPA contract or sponsorship or are subject to EPA regulations concerning risk assessments. The terminology and concepts described here also may be of assistance to other Federal, State, and local agencies as well as to members of the general public, including stakeholders, who are interested in cumulative risk assessment issues. The style and language used in this report were chosen so as to be understandable by as wide a variety of interested parties as possible, from the policy maker to the risk assessment scientist to the concerned nonscientist member of the general public. It is hoped that this report will be the first step in developing a broad scientific consensus about cumulative risk assessment, and that further guidelines and guidance will build upon this foundation.

1.3. Key Definitions in Cumulative Risk Assessment[3]

In this report, "cumulative risk" and "cumulative risk assessment" are defined as follows, assuming a defined population:

> **Cumulative risk:** The combined risks from aggregate exposures[4] to multiple agents or stressors.
>
> **Cumulative risk assessment:** An analysis, characterization, and possible quantification of the combined risks to health or the environment from multiple agents or stressors.

---

[3] In this section, a few basic definitions related to cumulative risk assessment are discussed. For a glossary of terms, the reader is directed to Chapter 5.

[4] See the box on the next page for a definition of aggregate exposure. Some references (e.g., Berglund et al., 2001) refer to this type of total exposure over time for a single stressor as "cumulative exposure." To avoid confusion, we have not used the term "cumulative exposure" in this report.

Several key points arise from this definition of cumulative risk. First, cumulative risk involves multiple agents or stressors, which means that assessments involving a single chemical or stressor are not "cumulative risk assessment" under this definition. Second, there is no limitation that the "agents or stressors" be only chemicals. "Agents or stressors" may be chemicals, of course, but they may also be biological or physical agents or even the absence of a necessity such as habitat. Third, this definition requires that the risks from multiple agents or stressors be combined. This does not necessarily mean that they be "added," but rather that some analysis should be conducted on if and how the effects or risks from the various agents or stressors interact. It also means that an assessment that covers a number of chemicals or other stressors but that merely lists each chemical with a corresponding risk without consideration of the other chemicals present is not an assessment of cumulative risk under this definition.

FQPA's Terminology Interpretations

The Food Quality Protection Act of 1996 [P.L. 104-170] discusses the addition of exposure for a single chemical across sources, pathways, routes, and time as *aggregate exposure.* To be consistent with that terminology, the Agency has elected to speak of multiple source/pathway/route *single-stressor* exposures and risks as "aggregate exposures" and "aggregate risks." The EPA Science Policy Council's Cumulative Risk Subcommittee has developed the following working definitions for single-chemical or single-stressor situations:

Aggregate exposure: The combined exposure of an individual (or defined population) to a specific agent or stressor via relevant routes, pathways, and sources.

Aggregate risk: The risk resulting from aggregate exposure to a single agent or stressor.

The definition of cumulative risk assessment follows from the definition of cumulative risk, but again there is a key point: cumulative risk assessments can be qualitative as well as quantitative.

Some examples of cumulative risk assessments as well as assessments that would not be considered as cumulative risk assessments are listed below. Each example presupposes a defined individual or population[5]:

1. **Single-agent or -stressor assessment.** Risks can be added or accumulated over time for a single agent or stressor across sources, environmental pathways, or exposure routes. This concept is consistent with "aggregate risk" in the terminology of the Food Quality Protection Act of 1996 (FQPA), shown in the box on this page. Although this type of assessment might conceivably be termed a cumulative risk assessment by some scientists, in this framework report such single-stressor assessments are termed "aggregate risk assessments." Examples might be a multisource assessment of benzene risk in a community or an assessment of individual risk to a

[5] Populations can be defined by geophysical boundaries, such as a watershed, or geopolitical boundaries, such as city or county limits, or by cultural, racial, economic, or other criteria within a certain geographic boundary such as a neighborhood. The definition of a population needs to be clear enough so that it can be agreed upon whether any specific individual is included in or excluded from the population.

specific pesticide from all uses combined. This type of assessment is not discussed in this report except to be referred to occasionally for clarity and contrast to cumulative risk assessments. There are several publications that discuss aggregate exposure and risk assessment in detail (e.g., ILSI, 1998, 2001; USEPA, 1999g).

2. **Multiple-stressor assessment.** Exposures can be accumulated over time, pathways, sources, or routes for a number of agents or stressors. These stressors may cause the same effects (e.g., a number of carcinogenic chemicals or a number of threats to habitat loss) or a variety of effects. A risk assessment for multiple stressors may evaluate the risks of the stressors, associated health effects or ecological impacts one effect or impact at a time or it may evaluate the combined risk from some or all the effects or impacts; in either case, it is considered to be a cumulative risk assessment.

A multiple-stressor cumulative risk assessment is distinct from a series of aggregate risk assessments because it considers any combined impact of the stressors, including the potential for interactions among stressors (e.g., synergism or antagonism). One example of a multiple-stressor, single-effect cumulative risk assessment would be the combined risk to an individual or population from a series of pesticides acting by the same mode of action and causing the same effect.

Another example would be a dioxin assessment, where toxicity equivalency factors (TEFs) are used to combine the toxicities of dozens of different congeners of chlorinated dibenzo-p-dioxins and dibenzofurans, resulting in a single estimate of risk for a specific effect from the combination of congeners (Eadon et al., 1986; Barnes et al., 1991).

Another example is a physician's use of a model derived empirically from epidemiological studies to estimate the probability of a woman's developing breast cancer over the next 10 years. The "stressors" in the example of the breast cancer model are those risk factors known to be correlated with that form of cancer, such as the woman's age at first childbirth, age at menarche, or having a previous biopsy with atypical hyperplasia. This example shows that stressors may not necessarily be chemical stressors, nor do they even need to be the same types of stressors. These models (discussed further in Appendix F) are in some ways quite different from the predictive risk assessments generally done for regulatory and other purposes.

Another type of cumulative risk assessment discussed in this report is the multiple-stressor, multiple-effects assessment. Again, stressors need not be limited to chemicals, nor do they even have to be the same types of stressors or have similar effects to be included in this type of assessment. For example, chemical, biological, radiological, and other physical and even psychological stressors can cause a variety of human health or ecological health effects. Assessing the risk for these situations is considerably more complex methodologically and computationally than for the examples of aggregate risk assessments or single-effect cumulative risk assessments given in the above paragraphs.

As complex as this may sound, there are several examples of this type of assessment. Although these analytical approaches may start with the stressors and predict the risk of effects, more generally these types of assessments start with a defined geographical area or defined population (e.g., a population damaged in some endpoint or due to a reduction in a resource value) and try to determine what stressors are important.

For example, cumulative ecological risk assessments such as those that have been conducted in the Columbia River Basin and the Chesapeake Bay focus on a number of observed adverse conditions, then attempt to determine, among all of the possible stressors, which particular combination is responsible for the observed adverse conditions (Barnthouse et al., 2000).

NRC (1994, Appendix I) lays out the general mathematics for a quantitative approach to multiple-stressor, multiple-effect assessments. Recently, Bogen (2001) used this approach to quantify combined risk of cancer and noncancer endpoints induced by the chemical trichloroethylene (TCE), including quantitative characterization of associated interindividual variability and associated uncertainty (including uncertainty regarding mechanism of carcinogenic action). Technical hurdles involved in implementing this approach include defining the set of relevant (preferably independent) endpoints and quantifying the likelihood of inducing each adverse health or ecotoxic response considered unacceptable as a function of the endpoints.

Another example of a type of multiple-stressor, multiple-effect assessment would be a cumulative community health risk assessment.

We believe that the definition of cumulative risk used in this framework report is consistent with the sense of most definitions of "cumulative," such as are included in NEPA or FQPA. A summary of the features and options of a cumulative risk assessment, by the definition used in this report, is given in the box on the next page.

1.4. The Cumulative Risk Assessment as a Tool for a Variety of Users and Purposes

As discussed in the introduction of this report, the results of an assessment should reflect the purpose for conducting the assessment. However, information from cumulative risk assessments can also serve a variety of other purposes. Insights gained may also be used to partly meet regulatory mandates and to help identify targets for enforcement actions, or they may be considered when shaping policy and regulation. Assessments may conceivably be used in long-term planning with regard to siting new sources of potential pollution in specific areas. Assessments also may be used for general educational purposes not directly related to an immediate decision on a course of action. Assessment results can help guide priorities for voluntary or regulatory action or mobilize community efforts to address concerns. They can be conducted retrospectively (to determine past or current risks), prospectively (to assess the risks of, say, proposed facilities), or even creatively (to design a development plan for a community). As helpful as results may be in any of these other uses, however, some consideration should be

given to the *appropriateness* of using the assessment for these purposes, given the objectives and scope of the assessment.

Risk analysis, including cumulative risk analysis, is conceptually an analytic-deliberative process (NRC, 1996). The analytic component includes rigorous, replicable methods that are evaluated under the agreed protocols of an expert community; the deliberative component is based on stakeholder value and judgment. Much of what is discussed in Chapter 2, "The Planning, Scoping, and Problem Formulation Phase," is deliberative in nature, which means it depends on input from experts other than those who know how to do risk assessments, including persons who are knowledgeable about a community and its values. Although much of Chapter 3, "The Analysis Phase," is given over to the analytic process, where risk assessment experts apply science to a problem, the deliberative aspect returns in Chapter 4, "The Risk Characterization Phase," especially where risks of different types are being evaluated and combined.

Cumulative Risk Assessment Features

Although many different types of exposures, stressors and other factors *can* be included, the definition of cumulative risk might be better understood by contrasting the featured and optional considerations. By the definition given above for this Framework report, the following features are included:

- Multiple stressors.
- Consideration of how the stressors act together rather than individually.
- Population-focused assessment. Although this does not mean that the assessment must start with a population and work "backwards" toward the source, it does mean that the population needs to be defined, and multiple stressors are assessed with regard to impact on that population, although not every individual will see the same (or all) effects.

Additional layers of complexity, such as those listed below, may or may not be addressed:

- Multiple durations, pathways, sources, or routes of exposure.
- Multiple effects or impacts.
- Nonconventional stressors or risk factors (e.g., lifestyle, access to health care). These in general need continued research.
- Quantification of risks.

Because of this analytic-deliberative process, the cumulative risk assessment can be applied to a variety of different problems where analysis of the overall impacts of multiple sources, stressors, pathways, or routes is necessary. It can be used as a regulatory analysis tool, such as in reviewing the overall impact of several different pesticides that act by the same mode of action (ILSI, 1999) or in NEPA analyses (CEQ, 1997). It can be used to analyze the overall impacts of permit decisions or the results of compliance with permits in a given community.

Cumulative risk assessment can also be used in a community-based assessment approach, as outlined in USEPA (1999f). The community-based environmental protection (CBEP) approach (see box on next page) encompasses both ecological and human health assessments. Cumulative risk assessment, being a population-based or place-based analytic-deliberative process, is ideal for CBEP-type applications.

Cumulative risk assessments are also applicable in ecological assessments. EPA's definition of cumulative ecological risk assessment is a process that involves consideration of the aggregate ecological risk to the target entity caused by the accumulation of risk from multiple stressors (USEPA, 1998b). A report by Foran and Ferenc (1999) discusses multiple stressors in ecological risk assessment and gives a good overview of the topic of cumulative ecological risk assessment.

Core Principles of Community-Based Environmental Protection

1. Focus on a definable geographic area.
2. Work collaboratively with stakeholders.
3. Assess the quality of all resources in a place.
4. Integrate environmental, economic, and social objectives.
5. Use the most appropriate tools.
6. Monitor and redirect efforts through adaptive management.

Source: USEPA, 1999f

When should a cumulative risk assessment be done? Recognizing that the scope and nature of a cumulative risk assessment may range from a very limited qualitative assessment of a local situation, to a comprehensive assessment of the cumulative risk patterns for a large community, to a national assessment conducted within one of EPA's programs, the simple answer is that one should be conducted whenever the combined impact of multiple stressors should be considered. Only experience with these assessments over a period of time will provide the wisdom needed to develop practical guidelines on this question.

1.5. The Broader Decision-Making Context for Cumulative Risk Assessment

Cumulative risk assessments may be used to form hypotheses that can be tested, but it is more likely that these assessments will be used as decision-making tools. The levels of decision making may vary widely, from a neighborhood group evaluating ways to improve or safeguard its health and environment to a Federal official weighing options for action at a much broader geographical level. Although the decision-making method is beyond the scope of this report, such decisions usually involve more than the basic science and analysis that make up the "scientific" part of risk assessment. Clemen (1996) notes that in one type of decision-making approach (called decision analysis):

> Managers and policy makers frequently complain that analytical procedures from management science and operations research ignore subjective judgments. Such procedures often purport to generate "optimal" actions on the basis of purely objective inputs. But the decision-analysis approach allows the inclusion of subjective judgments. In fact, decision analysis *requires* personal judgments: they are important ingredients for making good decisions.

Regardless of the type of decision being made or the decision-making approach, a cumulative risk assessment's analytic component is not the decision-making vehicle in itself. That is, "cranking out the numbers" will not be the sole basis for a decision. Although in some cases the estimated risks can weigh heavily in the decision, understanding the risk estimate is but

one factor in a broader decision-making process that includes risk management components such as technical feasibility, economic costs and benefits, political realities, and other analyses usually associated with the field of policy analysis (e.g., OMB, 2000; Freeman, 1999; Hattis and Gobel, 1994; Ashford et al., 1981).

EPA's Science Advisory Board (SAB) (USEPA, 2000a) has constructed a framework for what it terms integrated environmental decision making. The SAB noted that "The IED Framework recognizes that risks often are experienced simultaneously and are cumulative. . . ." It speaks of risk assessments in a very broad way and includes human health effects, ecological effects, and quality-of-life effects. The first phase ("Problem Formulation") and part of the second phase ("Analysis and Decision-making") of the IED essentially correspond to the three phases discussed in this framework report. Decision making—and the SAB's third phase, "Implementation and Performance Evaluation," are beyond the scope of this report.

The SAB report gives a good insight into the broader context for cumulative risk assessment and some of the aspects of the analytic-deliberative parts of the assessment. The analytical-deliberative process is discussed more in Chapters 2 through 4 of this report as these phases of the cumulative risk assessment process are examined.

NRC (1996) also provides much information on the analytic-deliberative aspects of a risk assessment and devotes a great deal of discussion to risk characterization. Needless to say, it is very important to apply cumulative risk assessment in the context of the decision or decisions to be made. This is most efficiently done by early and continued attention to the "risk characterization" step in the risk assessment process (NRC, 1996; USEPA, 2000c). The box in Section 4.1 summarizes some of the points made in the NRC report.

1.6. Organization of This Report

Figure 1-3 shows the basic structure of this report. Each of the three general process steps are described in detail in later chapters. The framework is organized to follow the outline in Figure 1-3, namely (a) a planning, scoping, and problem formulation phase (Chapter 2), (b) an analysis phase (Chapter 3), and (c) a risk characterization phase, where the interpretation of findings and explanation of the results are completed (Chapter 4). Chapter 5 is a glossary of terms, followed by references in Chapter 6. Additional information on selected resources and cumulative risk related topics are provided in the appendices.

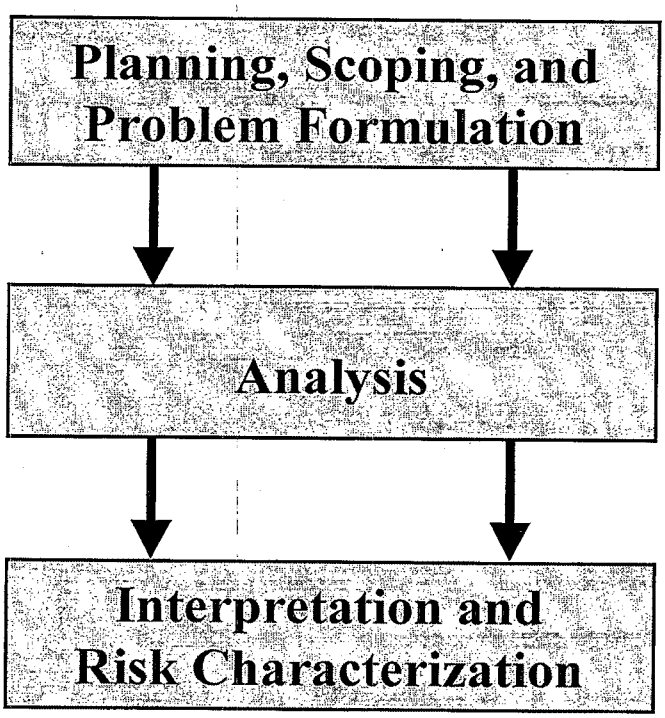

Figure 1-3. Framework for cumulative risk assessment.

2. THE PLANNING, SCOPING, AND PROBLEM FORMULATION PHASE

The first step in any risk assessment process is to define the problem to be assessed. This step has been called "problem formulation" (for example, USEPA, 1992b, 1997a, 2000a; NRC, 1996). It is a phase where "public officials, scientists, and interested and affected parties clarify the nature of the choices to be considered, the attendant hazards and risks, and the knowledge needed to inform the choices" (NRC, 1996).

The planning and scoping of an assessment are often thought to be part of the problem formulation phase, although EPA guidance (USEPA, 1997a) treats planning and scoping as activities that take place before problem formulation begins. Whether they are considered a separate phase or not, they take place at the very beginning of a cumulative risk assessment. For convenience, this chapter incorporates planning, scoping, and problem formulation into a single phase (see Figure 2-1).

2.1. Planning and Scoping

Risk assessments are conducted within some context, that is, they are usually conducted because of a regulatory requirement, a community need, a health crisis, or some other driving force. This context generates individuals or groups with interest in having the assessment done; several summary articles or books discuss the challenges of successful participation by these interested parties (e.g., Chess and Purcell, 1999; Frewer, 1999; Thomas, 1995). These parties may include public officials, risk experts, community leaders, or any number of others, including those, if any, who are legally mandated to be part of the process. Planning and scoping begins with a dialogue among these individuals or groups.

Among these interested parties will be a person or a group of people charged with making decisions about how a risk may be mitigated, avoided, or reduced. For the sake of simplicity, we call this person or group the "decisionmaker," or "risk manager[6]," and for ease of discussion will discuss the risk manager as if he or she were a single person.

During planning and scoping, risk experts (including those involved in assessing risk, such as ecologists, toxicologists, chemists, and other technical experts such as economists and engineers), and decisionmakers work together as a team, informed by stakeholder input, to develop the rationale and scope for the risk assessment and characterization.

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[6] We use the term "risk management" to include actions that the risk assessment team recommends or implements that are not taken by the risk assessment team, per se. These include actions to address the problems taken by others outside the process who may not be identified until the analysis is underway or complete.

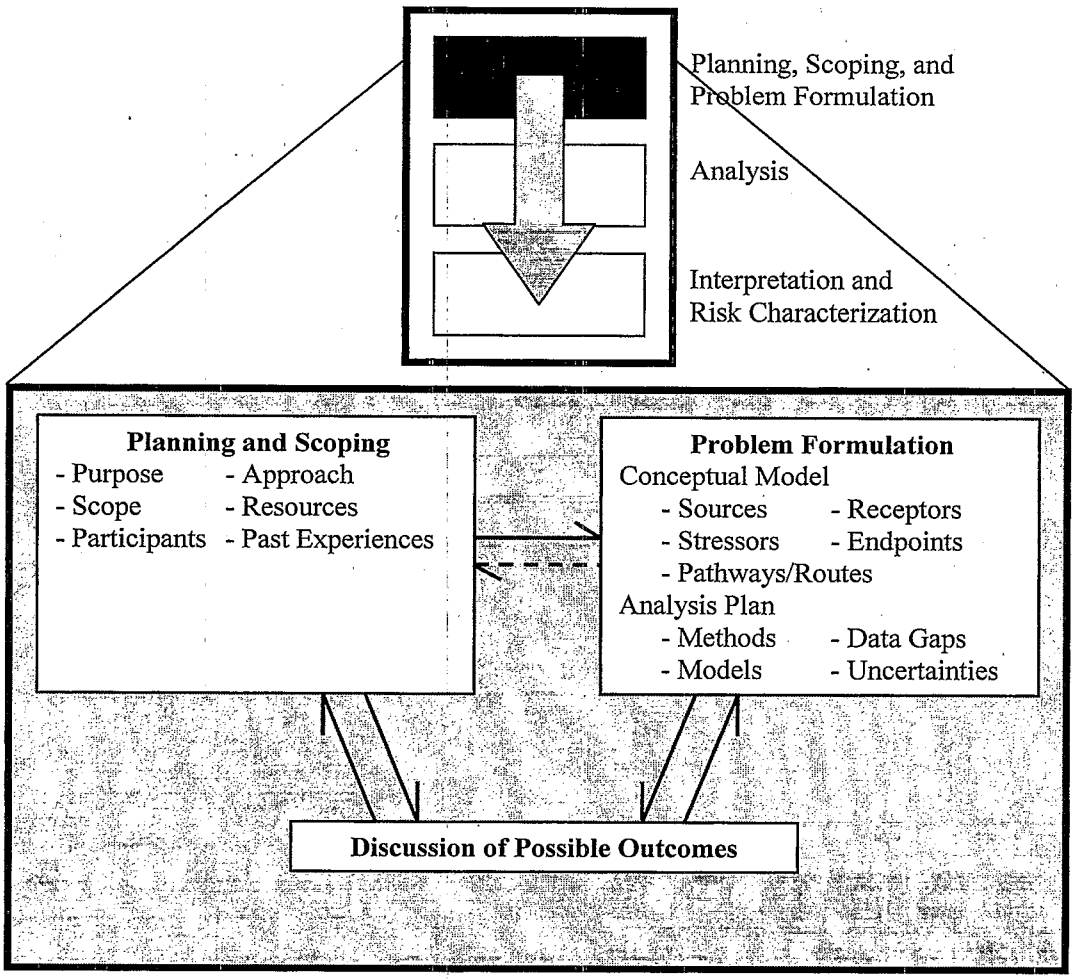


Figure 2-1. The Planning, Scoping, and Problem Formulation phase.

As part of the initial discussions concerning the need for a risk assessment, other "interested and affected parties" besides the risk manager and risk assessor may help define purpose, scope, and approach. This "risk assessment planning team" seeks agreement through extensive dialogue and discussion on what analytical and deliberative steps need to be taken and by whom, when, and why (USEPA, 2000a). USEPA (2000a) explains some of the roles of the various participants on the risk assessment planning team during the planning and problem formulation phase:

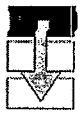
> Scientists play an important role in [this phase] by collecting, analyzing, and presenting data in such a way that all parties can appreciate the type and magnitude of the problem(s) under discussion. This activity will generally involve all four parts of risk assessment, including assessment of exposures

> experienced by special populations and/or ecological resources. Planning, scoping, and screening—including selection of endpoints of concern—also requires explicit input of societal values and stakeholder participation. For instance, while some of the ecological endpoints may be chosen because of their role in a valued ecosystem, there may also be ecological endpoints chosen because of their direct significance to society. Examples of the latter include both economically important species and 'charismatic' species. Similarly, in integrated decision-making, judgments may have to be made about diverse health endpoints, such as cancer risks in the general population and the risk of reproductive/developmental risks in children. While scientists can help characterize such risks, they are not uniquely qualified to set priorities among them and broader deliberation is essential. Finally, decision-makers also play an important role during problem formulation; in addition to bringing the scientific and other resources of the Agency to bear on the problem, they also should help to identify the range of potential decisions and viable management options, while examining economic, political, or other constraints on those options. Decision-makers also serve as managers of the overall process. (USEPA, 2000a)

Another role of the risk assessment planning team is documentation. The activities discussed in the following sections are important and should be documented by the team for several reasons. Written records can be referred to by assessors and attendees at public meetings. They can also help in responding to comments and in establishing a record for any later decisions or plans that need to be peer reviewed (USEPA, 2000d). The risk assessment planning team should consider whether or not the overall project is to be peer reviewed and, if so, what type of peer review will be conducted. The team should plan and execute the peer review at the appropriate time. A peer review by an independent review group will help not only to establish the validity of the science, but it can also provide neutral comments on some of the interpretations of the assessment.

In some cases, it may be useful for the stakeholders to appoint a "point person" to serve as the contact for communications. This is not to imply that stakeholders must speak with a single voice (which is not likely in any case), but that they have at least one person to help facilitate interactions and identify available technical resources and other sources of information. The Agency or stakeholders may also consider a public Web site for the project. A variety of resources can be posted, including cumulative risk tools and databases, project-related news, list of experts, glossary, reports, and related links. An online discussion forum could also be included on the Web site as a more interactive way of exchanging information with stakeholders.

Finally, while including stakeholders in the risk assessment process, a regulatory agency such as EPA should balance stakeholder participation with the Agency's need to retain the ability to carry out its responsibility to protect public health and the environment. For this reason, EPA will usually need to set some reasonable boundaries around the process to ensure that progress is being made in a timely and efficient fashion.



2.1.1. Defining the Purpose of the Assessment

As discussed in Section 1.5 above, the risk assessment should be developed to inform the risk management decision by constructing an appropriate, decision-relevant risk characterization. After the risk assessment planning team is assembled, the dialogue between the decisionmaker and risk experts begins with a discussion of risk management objectives and information needed to manage risks in the particular situation. The manager and assessment planning team should discuss any regulatory or legal basis for the risk assessment and what kind of information is needed to satisfy such requirements. If interested and affected parties are part of the risk assessment planning team, it is especially important that the entire team agree on the purpose of the assessment because a differing sense of purpose among the team will lead to problems later on.

The purpose and risk management objectives guide the risk assessment strategy (see box below for some possible management goals from which risk management objectives can be derived, e.g., in terms of key participants, data sources, selection of assessment endpoints, approach, and the schedule for developing the assessment). Other possible management goals include identifying options for control or abatement of hazards or risks, where decisions can then be made after considering costs and benefits of the various risk management options.

Possible Management Goals

The goals of risk management are varied. They may be risk related, aiming to:

- Reduce or eliminate risks from exposure to hazardous substances.
- Reduce the incidence of an adverse effect.
- Reduce the rate of habitat loss.

They may be economic, aiming to:

- Reduce the risk without causing job loss.
- Reduce the risk without reducing property values.

They may involve public values, aiming to:

- Protect the most sensitive population.
- Protect children.
- Preserve a species from extinction.

Source: Presidential/Congressional Commission, 1997

The previous discussion follows the typical situation where the risk manager is presented as an independent decisionmaker, such as a senior official in a regulatory agency who is responsible for establishing permit conditions for a facility of some type. There are situations, however, where the risk manager may be one of the interested parties outside the Agency, such as a local citizens' board. For example, mitigation of risks may not be significantly affected by any Agency or State permit decisions but will depend instead on local zoning decisions or on decisions that affect traffic patterns in a community. This is one of the reasons why the discussion of possible outcomes (discussed in Section 2.3) the final step in the planning and problem formulation phase is so important.

2.1.2. Defining the Scope of Analysis and Products Needed

Scoping a cumulative risk assessment effort involves defining the elements that will or will not be included in the risk assessment[7] (USEPA, 1997a). These include the stressors, sources, pathways, routes, populations, and effects or assessment endpoints to be evaluated.

As illustrated by the examples in the adjacent text box, the scope of a cumulative risk assessment may be narrow or broad. Initially, the risk assessment planning team should select the kind of risk information, exposure scenarios, and assessment issues that need to be covered. These should be directly linked to the risk-related questions being asked when establishing the purpose. Scope can be limited geographically (e.g., by political or ecological boundaries), environmentally (e.g., by assessing only certain media), demographically (e.g., by assessing only risks to children or asthmatics), legally (e.g., by statute or regulation), or by lack of methods or data in certain areas. The issue of background exposures to stressors should be discussed and agreements reached (see Appendix C).

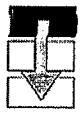
Examples of Cumulative Risk Assessment Scopes

- Health risks associated with the aggregate exposure (via all pathways and routes) to insecticides acting by a common mode of action.
- Human health risks associated with outdoor inhalation exposures of the general population to 33 priority air pollutants nationwide or via all routes to all pollutants present or being released from a hazardous waste site.
- Human health and ecological risks associated with multiple stressors resulting from developing a site or corridor of land for transportation, infrastructure, or a stationary facility.
- Human health risks for a specific neighborhood associated with exposure via all routes to all pollutants present or being released from a set of adjacent sources, including several industries, two hazardous waste sites, traffic, and a municipal landfill.

An adequate assessment scope should make it clear what is included in and what is excluded from the assessment. Care should be taken to reconcile the limitations of the scope with the list of questions to be answered in the statement of purpose. If, for example, data limitations preclude addressing certain questions outlined in the purpose, the list of questions should be modified and the risk assessment planning team agree to the narrower scope of the assessment. Defining the scope of an assessment is a process that can include both analytical and deliberative aspects.

The reasons for choosing the particular scope of the assessment and the manner in which the assessment will address the questions posed in the purpose statement should be stated explicitly. Defining the scope of the assessment should include details on the limitations of resources, limitations of data, the impact of risk elements on the risk estimate (i.e., some pathways may be seen as having negligible impact on the risks related to the questions being addressed), and limitations of the methods available. In cases where an element of risk is likely

[7] An assessment that looks at all stressors over a period of time for a specific population would be a "total risk" assessment, which is difficult to perform with our current methods.



to be important but no valid data are available, the risk assessors highlight this deficiency or use judgment or assumed values to approximate the missing data. Such judgments and approximations should be clearly documented and explained to the manager in the risk characterization.

Once the elements (sources, stressors, populations, etc.) have been identified by brainstorming with all the participants, the participants should discuss the need for and availability of technical information and how such information might affect the overall uncertainty of the assessment. Using input from the risk assessor, the risk assessment planning team should determine what elements will and will not (or can and cannot) be included in the risk assessment. Some of the stakeholder concerns may not be suitable for analysis by risk assessment, so other expertise and evaluation may be required to provide this additional analysis. Information gathered at this stage is preliminary and may be modified during the analysis phase. Identification of potential stressors, populations to be assessed, and potential effects are all part of the scoping process and help define the method of approach.

Stressors can include physical (including radiological) stressors or chemical or biological agents that may cause an adverse effect. The sources of the stressors can be human activities in sectors of society (e.g., manufacturing, transportation, agriculture, land development), personal activities (e.g., smoking, diet, and other lifestyle activities), or natural phenomena (e.g., forest fires, floods). Stressors that are not physical, chemical, or biological, such as economic or other quality-of-life stressors, may also be identified, but good techniques for including the effect these have on risk currently may not exist.

Population elements are usually entities that are at risk, for example, communities, portions of ecosystem functions (e.g., those species that provide food for others within the food chain), or vulnerable subpopulations such as persons with certain diseases or persons at vulnerable life stages, such as children. The more specifically these can be defined, the more focused the analysis can be. This will be helpful in interpreting the results of the assessment.

2.1.3. Agreeing on Participants, Roles, and Responsibilities

The risk assessment planning team will usually recommend other groups or individuals who should participate in the assessment planning, scoping, and risk analysis phase. Depending on the schedule, approach, and level of effort envisioned for the risk assessment, there may be no additional participants or there may be many. The analytic portions of the assessment will usually require substantial technical expertise. Some disciplines that may be pertinent include toxicology, epidemiology, ecology, exposure assessment, fate and transport modeling (e.g., indoor and outdoor air, surface and drinking water), computer science (including geographical information systems [GISs]), chemistry, biology, various engineering fields (e.g., chemical, mechanical, industrial, civil), economics, sociology, and others.

For the deliberative portions of the assessment, it may be that a number of stakeholders and other interested parties should be considered for participation (see box for examples). For community-based assessments, in particular, it is important that community involvement be sought and encouraged. The Presidential/Congressional Commission on Risk Assessment and Risk Management (PCCRARM, 1997) suggests the following questions to identify potential interested or affected parties (stakeholders):

Examples of Possible Interested or Affected Parties (Stakeholders)

State governments	Affected industry
Tribal governments	Civic organizations
Local governments	Business owners
Community groups	Trade associations
Grassroots organizations	Labor unions
Environmental groups	Public health groups
Consumer rights groups	Academic institutions
Religious groups	Outdoors clubs
Fishers and hunters	Impacted citizens
Civil rights groups	Other federal agencies

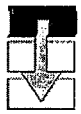
Source: Adapted from USEPA, 1999b

- Who might be affected by the risk management decision? (This includes not only groups that already know or believe they are affected, but also groups that may be affected but as yet do not know it.)
- Who has information and expertise that might be helpful?
- Who has been involved in similar risk situations before?
- Who has expressed interest in being involved in similar decisions before?
- Who might be reasonably angered if not included?

The importance of involving stakeholders in risk assessment is being increasingly recognized (e.g., NRC 1996; PCCRARM, 1997; USEPA 1996a, 1997a, 1998a, 1999c, 1999f, 2000a). The Commission's suggested guidelines for stakeholder involvement are shown in the box on the next page.

There are several issues concerning the stakeholders' capacity to participate that should not be overlooked by the risk assessment planning team. First, some stakeholders may need training to be able to participate in technical and risk management discussions. Second, as noted in the box on the next page, some stakeholders may require incentives such as travel funds or lodging at sites of meetings outside the area where they live. The risk assessment planning team, along with the potential source of funds for such incentives, should decide to what extent, if any, such incentives can be provided, based on the scope, level of effort, and financial constraints of the risk assessment project.

The roles and responsibilities of technical and nontechnical participants (i.e., ground rules for participants) should also be proposed by the planning team, depending on the schedule, approach, and level of effort that is envisioned for the risk assessment. There will be several key



Guidelines for Stakeholder Involvement

- Regulatory agencies or other organizations considering stakeholder involvement should be clear about the extent to which they are willing or able to respond to stakeholder involvement before they undertake such efforts. If a decision is not negotiable, do not waste stakeholders' time.
- The goals of stakeholder involvement should be clarified at the outset and stakeholders should be involved early in the decision-making process. Do not make saving money the sole criterion for success or expect stakeholder involvement to end controversy.
- Stakeholder involvement efforts should attempt to engage all potentially affected parties and solicit a diversity of perspectives. It may be necessary to provide appropriate incentives to encourage stakeholder participation.
- Stakeholders must be willing to negotiate and should be flexible. They must be prepared to listen to and learn from diverse viewpoints. Where possible, empower stakeholders to make decisions, including providing them with the opportunity to obtain technical assistance.
- Stakeholders should be given credit for their roles in a decision, and how their input was used should be explained. If stakeholder suggestions were not used, explain why.
- The nature, extent, and complexity of stakeholder involvement should be appropriate to the scope and impact of a decision and the potential of the decision to generate controversy.

Source: Presidential/Congressional Commission on Risk Assessment and Risk Management, 1997

points in the risk assessment process where stakeholder input will be critical, such as agreement on purpose, scope, and approach. Each project should define and approve a list of critical points for stakeholder input. The team may even decide to assign stakeholders to subgroups that have specific tasks, such as understanding the technical information and reporting back to the larger group, elevating and clarifying stakeholder issues as needed, or providing information and facts to their peers and to the analysts.

Sometimes citizens choose not to participate because they feel that they will not influence the outcome, that the issue is too complex or technical, or that the effort is too great or because the decision process is unclear (USEPA, 2001c). Moreover, despite the increased emphasis on stakeholder participation, there are instances where large-scale stakeholder involvement may not be appropriate. EPA (as the decisionmaker) should determine whether, and to what degree, stakeholder involvement in a cumulative risk decision will be useful and what objectives it may accomplish. There is a continuum of objectives that may apply to individual cases, from exchanging information on one end, through obtaining stakeholder recommendations, to developing agreements for joint activities at the other end (USEPA, 1998g).

Many of the activities and much of the data needed for cumulative risk assessment draw upon broad expertise, experience, and legal mandates found not only in EPA, but in other public health agencies and academia. The most successful cumulative risk assessments will likely be those where cooperation among organizations (Federal, State, private, environmental, academic, etc.) leads to use of the best data and tools for the various parts of the assessment.

2.1.4. Agreeing on the Depth of the Assessment and the Analytical Approach

The analysis approach (discussed further in Section 2.2.3 and Chapter 3) may fall anywhere on a continuum from relatively unsophisticated methods that rely heavily on default (and often conservative) assumptions, and consequently have greater uncertainty, to increasingly refined assessments in which data are substituted for assumptions and uncertainty is reduced. Some of the factors that go into deciding on the approach and associated plans for data collection include the level of uncertainty in the risk estimates that is acceptable to the participants, the intended use and audience for the assessment, the time and money resources available, and the amount, quality, and accessibility of data.

Cumulative risk assessments, because of their nature, may require more attention to time, space, and route of exposure than do many traditional assessments, and methods should be chosen, if available, to accommodate these needs. In making the decision on approach, there will need to be an understanding of both the level of effort necessary for conducting the assessment selected, with an insight to alternatives, and the features and limitations of the selected approach in comparison to other approaches.

2.1.5. Agreeing on the Schedule and Resources Available

Schedule and resources are often interrelated. They may also determine whether the work is performed in-house by the organization or team desiring the assessment or by a contractor or other external source. The need to meet external deadlines or to coordinate with the schedules of other organizations may become overriding factors in defining what will be prepared. Assessments that require short-term, low-budget efforts or preliminary screening assessments may not have the scope, time, or resources for extensive stakeholder involvement. When there is extensive stakeholder involvement, it is especially important that a budget and time schedule be developed and known by all participants.

2.1.6. Review of Lessons Learned

Much time and effort can be saved by taking the advice of those who have already been through this process or similar processes. Risk assessment reports will often have a review chapter of lessons learned (or, "if I had to do this over again, I would. . . ."). We have tried to include some discussion of recent Agency experiences to illustrate parts of this framework report. In addition, the reader is encouraged to find similar advice in other reports (e.g., USEPA, 2002b). For example, EPA's Office of Water has conducted several watershed studies over the past decade and has compiled a Web page with lessons learned (USEPA, 2001d) (see box on the next page for one of the lists). Even though not all studies were cumulative risk assessments, much of the wisdom gained is relevant.

Reed Holderman's Lessons Learned

(California Coastal Conservancy,
Santa Ynez Watershed)

1. Be sure that [the project] is needed, and if it is, build community support for it before proceeding.

2. Invite everyone into the process and ask political leaders to select the steering committee. Otherwise, people will ask, "Who appointed you?"

3. Don't be presumptuous. On the Santa Ynez River, we assumed everybody would appreciate a well thought out scope of work, budget, and schedule. Wrong. They said it only proved that the whole thing was a set-up. Next time, let [the whole planning team] figure it out!

4. When the majority of stakeholders tell you that they want to deal with their issue first, believe them. I remain convinced that our failure to sustain interest in the Santa Ynez River plan was primarily because we were not willing to assist the County in carrying out its proposed channel-clearing activities in the Lompoc valley as a separate and distinct project.

5. Do whatever you can to break down barriers and perceptions people have of each other. Be creative. Family BBQs, softball games, and parties have done wonders to improve relationships among stakeholders and build trust.

6. Maintain constant communication among stakeholders throughout the process—and especially in the beginning—to pass information along, answer questions, or deal with rumors. Whether it's through regular meetings, newsletters, web sites, phone trees, or all four, good communication is a must.

7. And finally, line up your money and in-kind services in advance of starting your [assessment] project, or else two bad things will happen: (a) your stakeholders will buy into a process and scope of work only to find out they can't afford it; and (b) you will spend more time looking for cash than participating in the planning process. Either way, you lose.

Source: USEPA, 2001d

2.2. Problem Formulation, Conceptual Model, and Analysis Plan

One outcome of the problem formulation phase is a conceptual model that is intended to identify relevant stressors, sources, pathways, exposure routes, receptors, and effects and the relationships among them. The conceptual model serves as a basis for the analysis plan, which is used to focus the analysis phase of the assessment.

2.2.1. Problem Formulation

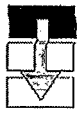
Problem formulation is a systematic planning step that identifies the major factors to be considered in a particular assessment. It is linked to the regulatory and policy context of the assessment. Problem formulation is an iterative process within which the risk assessor develops preliminary hypotheses about why adverse effects might occur or have occurred. It provides the foundation for the technical approach of the assessment. The outcome of the problem formulation process is a conceptual model that identifies the stressors, the population exposed, and the assessment endpoints that will be addressed in the risk assessment and describes the relationships among them. One of the major differences between a cumulative risk assessment and a more traditional, single-chemical assessment is that in a cumulative assessment special attention should be given to identification of stressors and endpoints and the relationship between them.

The box below shows desired outputs from the problem formulation phase of an environmental decision-making exercise. Although such an exercise is not precisely the same as a risk assessment, some of the outcomes are applicable, depending on the scope of the assessment.

The Science Advisory Board's Desired Outputs for Problem Formulation

- The initial goals for the decision-making exercise, including environmental goals to be achieved
- Which environmental problems/stressors/systems will be included and which will not, and the reasons for these decisions
- The health, ecological, and quality-of-life effects of concern
- The spatial, temporal, and organizational dimensions to data analysis
- Scoping of the uncertainties involved and research needed to significantly reduce critical uncertainties
- Initial review of the range of options available to reduce risks, considering likely economic, political, or other constraints
- The endpoints upon which the condition of the ecological, human health, or societal systems ultimately will be judged

Source: USEPA, 2000a



2.2.2. Developing the Conceptual Model

A conceptual model includes both a written description and a visual representation of actual or predicted relationships between humans (or populations or population segments) or ecological entities and the chemicals or other stressors to which they may be exposed.

Conceptual models represent many relationships and may describe primary, secondary, or tertiary exposure pathways. The model is developed by the risk assessor and may include input from other experts (including stakeholders). The model narrative should distinguish—to the extent possible—between what is known or determined and what is assumed. Also, it should include a discussion of uncertainties in the formulation of the assessment and state how the assessment is cumulative, that is, for which sources, stressors/agents, pathways/exposure routes, receptors/populations, and endpoints. In some cases, conceptual models will be submitted for peer review.

A general conceptual model (Figure 2-2) defines the components of such a model and shows the theoretical pathways and routes of exposure between the stressors (and sources of stressors) and effects (endpoints) for human and ecological receptors. The conceptual model includes factors and endpoints that may not be analyzed in the risk assessment but may be evaluated in the overall decision-making process.

The conceptual model and the associated narrative show the basic rationale for the decisions made in pursuing a particular course of action. It provides a record of decisions for future reference during risk analysis and characterization and communication of the risk management decision. It is also valuable as a risk communication tool both within the Agency and in interactions with the public. The conceptual model provides a scientific or technical work product that includes (1) the scientific rationale for selecting the stressors, sources, receptors, exposed populations, exposure or environmental pathways, endpoints, or effects; (2) the scientific, technical, economic, or sociologic basis for the construction of the conceptual model; and (3) the scientific implications of additional data gathering.

Figure 2-3 is an example of a conceptual model from the National Air Toxics Assessment (NATA).[8]

It is not inconceivable, given the deliberative nature of the process of developing a conceptual model, that more than one model will be considered. If the team decides to ultimately use more than one model and to evaluate each as part of hypothesis testing, a careful consideration of time and monetary resources should be made, as well as a very careful consideration of how the results will be interpreted (see Section 2.3).

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[8] NATA is the technical support component of EPA's National Air Toxics Program (64FR38706-38740; USEPA, 2001e).

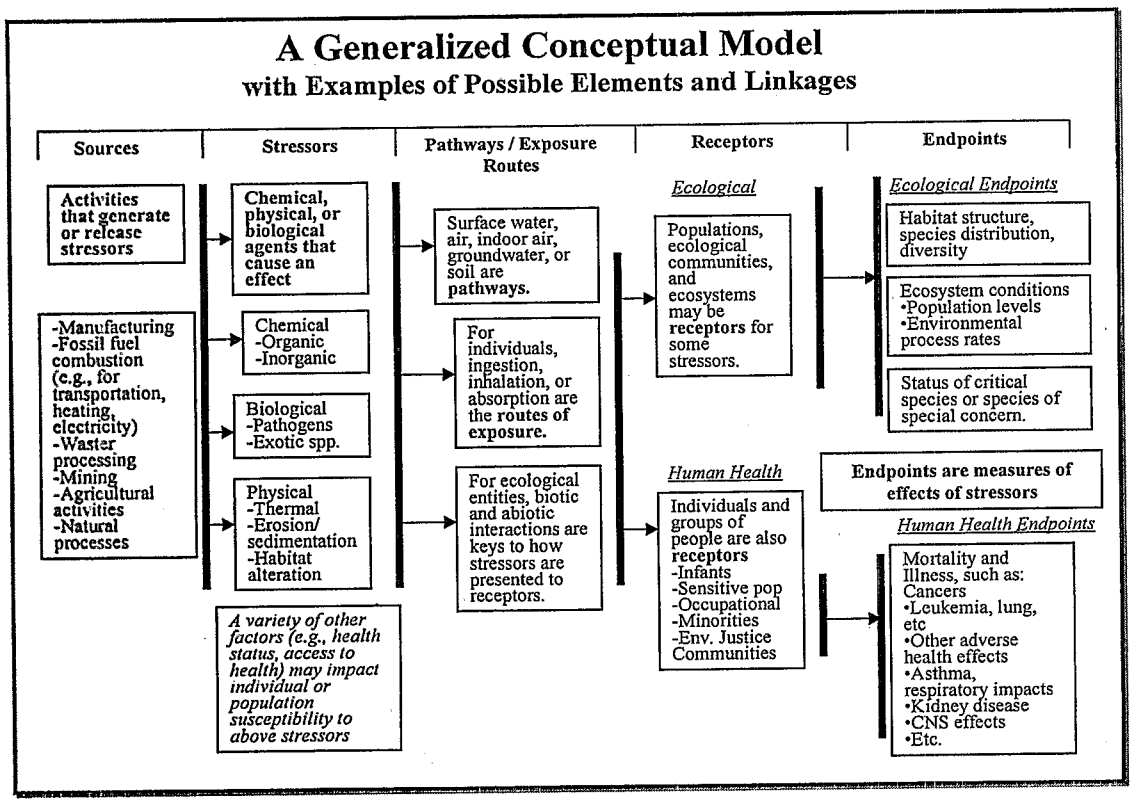


Figure 2-2. An example of a generic conceptual model (adapted from USEPA, 2002b).

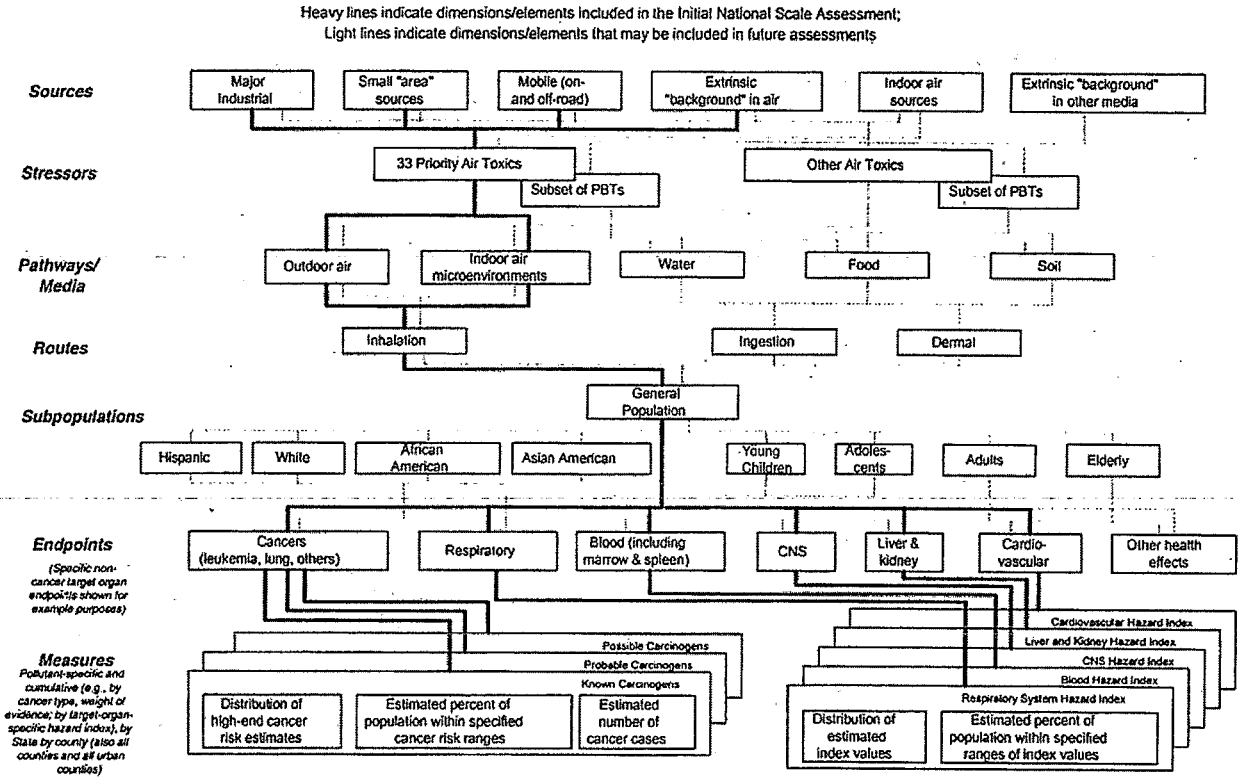


Figure 2-3. Specific conceptual model for a complex project, OAQPS' National Scale Air Toxics Assessment.

PBT = persistent, bioaccumulative, and toxic
CNS = central nervous system

Source: USEPA, 2001e

2.2.3. Constructing the Analysis Plan

The analysis plan is the final stage of the planning and scoping process (see discussion in USEPA, 1998b). It describes how hypotheses about the relationships among the sources, stressors, exposure conditions, populations, and adverse effects/endpoints (see box) presented in the conceptual model and narrative will be considered during the risk analysis phase of the assessment. The plan includes the rationale for which relationships (referred to as "risk hypotheses" in USEPA, 1998b) are addressed, methods, models, and a discussion of data gaps and uncertainties. It also may include a comparison between the level of confidence needed for the management decision and that expected from alternative analyses in order to determine data needs and evaluate which analytical approach is best. In some cases, a phased or tiered risk assessment approach can facilitate management decisions, particularly in cases involving minimal data sets.

Important Details for an Analysis Plan

Sources:
Identification of sources to be included and methods and associated data for including them.

Stressors:
Identification of stressors to be included and methods and associated data for including them.

Clarification of direct- and indirect-acting stressors.

Exposure Conditions:
Specification of exposure conditions to be assessed, along with methods.

Populations:
Identification of the populations on which analysis will focus.

Endpoints or Adverse Effects:
Identification of one or more unique, well-defined endpoint for analysis. Note that a concept such as "health of the community" is not a well-defined endpoint.

Identification of linkages between assessment endpoints and measurable attributes.

Specification of those endpoints or exposures that will be measured directly and those that will be estimated or for which surrogates will be used.

Identification of common endpoints/effects for groups of stressors for which risks or impacts are to be combined.

Description of methods to be employed for combining risks in terms of endpoints.

The analysis plan provides a synopsis of measures that will be used to evaluate risk hypotheses (as shown in Appendix D). The plan is strongest when it contains explicit statements of how measures were selected, what adverse effect (or assessment endpoint) they are intended to evaluate, and which analyses they support. Uncertainties associated with selected measures and analyses and plans for addressing them should be included in the plan when possible. The analysis plan can be a brief summary of the key components of the risk assessment and how each component will be measured or calculated.

In a cumulative risk assessment, a key aspect is considering whether and how multiple stressors interact or act together in contributing to risks; thus, some early thought should be given to the strategy for addressing this aspect of the assessment. The strategy should address methods to be employed for considering potential joint action of multiple stressors on a single endpoint as well as whether

the assessment will attempt to describe cumulative impact on multiple endpoints. The discussion of this issue in the analysis plan can include both qualitative and quantitative approaches (see Chapter 3).

As with the conceptual model, societal importance, complexity, and available data and resources will determine the degree of sophistication and detail needed in the analysis plan. Key data gaps should be identified. The plan should also include thoughts about how to fill the information needs in the near term using existing information, in the midterm by conducting tests with currently available methods to provide data on the agent(s) of interest, and over the long term to develop better, more realistic understandings of exposure and effects and more realistic test methods to evaluate agents of concern. The plan should explain how measures were selected, what they are intended to evaluate, and which analyses they support. Uncertainties associated with selected measures and analyses and plans for addressing them should also be explicitly stated.

The analysis plan should include (where feasible) milestones for completing the risk assessment. The plan may be revisited and revised periodically. If new information is acquired, such revisions may refine hypotheses of exposure and toxicity, modify the risk hypotheses addressed, or compare public concerns with the projected risk management options.

2.2.4. An Early Look at Uncertainty

In preparing the conceptual model and analysis plan, there should be some early thinking about uncertainty. In Section 4.2.1, there is a discussion of different types of uncertainty that should be considered in the analysis: (1) parameter uncertainty (uncertainty about technical, scientific, economic, and political quantities), (2) model uncertainty (uncertainty about the appropriate functional form of technical, scientific, economic, and political models), and (3) disagreements among experts (e.g., about the values of quantities or the functional form of models, as when different health scientists use different forms of dose-response models). These considerations are important for interpreting the results of the study and should be considered in the selection of methods as part of the planning, scoping, and problem formulation process.

The first of these uncertainties facing the planning team is the so-called epistemological uncertainty (not yet even knowing what questions to ask). It is likely that in planning any complex assessment, some questions will only become evident after the data collection or analysis has begun. It is therefore important that the planning team make provisions for revisiting the analysis plan—or even the conceptual model—at intervals during the process. Even more helpful would be an agreed-upon mechanism for changing the analysis plan or conceptual model before the need for revision arises, as it almost assuredly will.

The second general aspect of uncertainty that should be dealt with in the planning, scoping, and problem formulation phase is "acceptable uncertainty." How much uncertainty is the planning team willing to accept in the results of the study? Typically, this is a very difficult question for risk assessors and decisionmakers to answer, but it is a key question that enormously affects the cost and usefulness of the study.

At one end of this acceptable uncertainty spectrum are risk assessments that are based only on readily available information. At the other end is an assessment that starts with carefully reasoned and detailed quality assurance parameters, leading to specific data being accepted or rejected for the study based on predetermined quality assurance guidelines. This process in turn leads to results with known and acceptable uncertainties, but it may either require expensive data collection or cause the study to fail when none of the data meet the quality assurance requirements. The planning team should decide where on this spectrum it wants to be for the study under consideration and whether the results will allow meaningful decisions.

Again, the decision on acceptable uncertainty is difficult, but consideration early in the process will improve the potential for producing an analysis suited to the needs of the stakeholders.

2.3. Ecological versus Human Health versus "Integrated" Cumulative Risk Assessment

Cumulative risk assessments may include both human health and ecological aspects. Several reports have dealt with cumulative ecological risk assessment in some detail (e.g., Foran and Ferenc 1999; Ferenc and Foran 2000; USEPA 1998b). USEPA (2002c) noted some of the major differences between human health and ecological assessments (see list below), and these differences need to be considered when planning a cumulative risk assessment that includes both aspects:

- Ecological systems are not as well known biologically as are human health systems, either at the population and at the individual level;
- For this reason, and because biological communities and ecosystems are inherently more complex, ecological risk assessment requires more preliminary analysis and deliberation regarding endpoints and protective standards;
- Ecosystems, habitats, and ecological communities have traits and properties that individuals do not or that are not applicable to individuals or populations;
- Ecological risk assessment has been generally applied to populations, not individuals, whereas the reverse is true for human health risk assessments; and
- Ecological risk assessment should assess risk at multiple levels or organization, that is, the molecule, cell, organism, population, community, and ecosystem.

The World Health Organization (WHO, 2001) has published approaches to integrating human health and ecological risk assessments to improve data quality and understanding of cumulative risks for decision making. The organization's approach includes an integrated framework (modified from USEPA, 1998b) and case studies.

Many tribal cultures view ecological and human health in an integrated way such that they cannot be easily separated. Similarly, there is some effort (especially in Canada) toward integrating human health and ecological assessment as well as decisionmaking in a field known as "strategic environmental assessment" (Bonnell and Storey, 2000). This approach has not been applied widely in the United States, and it remains to be seen how it will develop in the next few years.

2.4. The Final Step Before the Analysis Phase: Discussion of Possible Outcomes

Before the analytical efforts of the cumulative risk assessment are started, it is useful for the entire team to hold some preliminary discussions about the possible results and their implications. Given that statutory mandates, regulations, property rights, or due process may constrain or define most or all acceptability criteria, what conclusions of the team will be associated with various results or risk levels? For example, for a risk assessment team with members from the community, industry, and local and other government entities, what would happen if the assessment shows risk levels to be "low"? Would members accept this? Conversely, if "unacceptable" risks are determined, will all team members accept the results and their potential responsibility to do something about that risk? Do team members understand the limitations of the information to be generated?

Discussions like these will help determine whether the assessment can really address the questions of the team. If not, the assessment may not be worth doing as planned. If members of the team will not accept the possibility of a range of results, then it is important to reopen the entire planning and scoping discussion before anything is done in the analysis phase, because the planning and scoping phase has not been satisfactorily completed. Although it is not necessary to have unanimity among stakeholders before proceeding with the plan, knowing where some of the potential disagreements may occur after the analysis and risk characterization phases are started allows the stakeholders as a group to plan beforehand for how such disagreements will be addressed, should they occur. Although it is possible to ensure that all stakeholders have been heard and their opinions given due consideration and weight, that does not necessarily mean that all of them will get what they want.

As an example, USEPA (2000f) is a case study where the stakeholders thought they had agreement on roles, responsibilities, and approach, only to find that the group acrimoniously splintered after the analysis results came back. The Baltimore report contains valuable lessons learned in the area of stakeholder disagreements and agendas and can provide some insight for planning teams.[9]

Discussions just prior to the analysis phase may lead to an assessment that is very different from the one originally envisioned. For example, in the case of the cumulative risk initiative for Cook County (IL) and Lake County (IN) (see box on next page) the original plan was for a quantitative cumulative risk assessment, but because of the lack of some critical information, the scope was changed. This led to an assessment that, although not as broad as in the original plan—and that did not even directly calculate risk—had better stakeholder buy-in and a better chance of success in providing useful information.

Finally, it should be acknowledged by all practitioners of cumulative risk assessment that in the current state of the science there will be limitations in methods and data available. It will

[9] This case study, along with several others, will be examined more fully in followup work to this framework report.

Cumulative Risk Initiative (CRI) for Cook County (IL) and Lake County (IN)

(formerly the Chicago Cumulative Risk Initiative, CCRI)

CRI BACKGROUND AND OVERVIEW

In 1995 the Chicago Legal Clinic and 11 Chicago-area community advocacy groups filed a petition under the Toxic Substances Control Act requesting that the EPA Administrator prohibit or further regulate emissions from eight proposed or constructed incinerators in the Chicago metropolitan area and Northwest Indiana. The petitioners believed that neither current statutes nor local siting laws adequately addressed cumulative impacts of multiple sources of toxic pollutants in a geographic area. They requested that the Administrator restrict emissions of dioxins, furans, mercury, lead, and cadmium from these sources. In May 1996 the petition was withdrawn in response to an EPA offer to participate in an investigation of multimedia pollutant impacts in Cook County, Illinois, and Lake County, Indiana. This effort became the CRI. A CRI is an attempt to investigate cumulative loadings and hazards from pollutant sources, to develop community-based activities to help address these concerns, and to use analytic results to help prioritize use of regulatory agency resources. EPA and the petitioners agreed to a four-phase project: (1) an environmental loadings profile (EPA 747-R-1-002); (2) a petitioner risk workshop (completed); (3) a hazard screening assessment (peer review draft available January 2002); and (4) a risk-hazard management response.

HAZARD SCREENING ASSESSMENT

The CRI hazard screening assessment was authored primarily by Argonne National Laboratory, with input from local, State and Federal participants. Reflecting stakeholder deliberations, the report focuses on cumulative hazard (not "risk" as typically defined by EPA) associated with noncriteria air pollutants ("air toxics") in the two-county study area. It relies on "off-the-shelf" air pollutant information, including EPA's Toxics Release Inventory, Cumulative Exposure Project, Regional Air Pollutant Inventory Development System, and outdoor air monitoring data. Emission estimates are "toxicity weighted," and modeled/monitored outdoor air pollutant concentrations are compared with reference values to develop hazard index-like ratios. The ratios or toxicity-weighted emission estimates are used to derive indicators of cumulative hazard and then mapped over study area locations. To identify geographic areas where potentially elevated hazards and individuals with potentially greater susceptibility are collocated, another part of the study assembles pollutant hazard information and data on existing human disease rates and indicators.

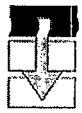
PRELIMINARY LESSONS LEARNED

1. A major planning/scoping/problem formulation effort by a broad group of stakeholders narrowed the scope of the CRI hazard screening assessment and seemed to increase stakeholder "buy-in" with the process. This was valuable, given the complexity, expense, effort, time requirement, and difficulty encountered in addressing even the narrowed scope.

2. Large data gaps make risk and hazard assessment of environmentally relevant chemical exposures highly uncertain, even for single agents. Expanded assessments that address cumulative risk considerations (e.g. mixtures, developmental toxicity, nonchemical agents) are a better match for real-world circumstances but require acknowledgment of even more uncertainty.

3. Obtaining and managing input from a large group of technical stakeholders is cumbersome and time-consuming, but that group's perspective and expertise greatly improved the CRI assessment.

4. Given that the National Research Council's 1983 four-step "framework" required several years for broad use and acceptance in the United States, the greater complexity of cumulative risk (for CRI, cumulative *hazard*) assessment suggests that an equally long period may be needed for terminology standardization, refinement of approaches, and development of consensus methods.



be important to identify these limitations and discuss them frankly in the cumulative risk assessment report. Data limitations may be somewhat mitigated by qualitative information; the collection of qualitative data may be valuable in cumulative risk assessment. Still, limitations in methods or data should not be seen as a convenient reason for completely ignoring or not posing questions for which stakeholders may be seeking answers. Lack of an appropriate methodology may indeed be a reason why certain questions cannot be addressed in the analysis phase, but capturing the questions and having some discussion about why the questions could not be addressed in the assessment is often helpful.

3. THE ANALYSIS PHASE

The analysis phase (Figure 3-1) is primarily an analytic process in which risk experts apply risk assessment approaches to evaluating the problem at hand.[10] The risk assessment paradigm most widely used by risk assessors during the past two decades was first documented by the National Research Council (NRC) (NRC, 1983). It consists of four parts: hazard identification, dose-response assessment, exposure assessment, and risk characterization. This paradigm was developed when almost all risk assessments were being conducted on single chemicals. Nevertheless, it is a useful place to start when considering cumulative risks.

This framework follows the NRC risk assessment paradigm in all respects except that the exposure and hazard/dose-response components should be evaluated together rather than separately. As a prerequisite to using this framework, assessors considering cumulative risk assessments should be familiar with the 1983 NRC risk paradigm as well as the various EPA risk assessment guidelines (see text box titled "EPA's Risk Assessment Guidelines" in Section 1.1).

In both single-stressor and multiple-stressor risk assessments, the analyst will look at hazard and dose-response relevant to the stressor(s) of interest and perform an analysis of exposure(s) to those stressor(s). This chapter begins with a basic discussion of this general process and its basic ingredients (Section 3.1). The second part of this chapter (Section 3.2) discusses some of the situations that arise in cumulative risk assessment, methods currently available for addressing them, steps in the process, and some limitations to these methods. Finally, Section 3.3 identifies areas of ongoing work that are particularly relevant to cumulative risk assessment.

3.1. General Process

In developing the conceptual model and analysis plan (see Section 2.2), the scope of the assessment was specified (see example in box on page 36). Some of the aspects of scope include stressors, sources, pathways and media, exposure routes, populations and subpopulations, endpoints, and measures.

The analysis plan should specify how data, modeling, or assumptions will be obtained, performed, or defined for all of the details concerning the characterization of exposure of the defined population and subpopulations to the defined set of stressors. Additionally, the analysis plan specifies the strategy for obtaining and considering hazard and dose-response

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[10] Although the analysis phase is primarily an analytic process, with heavy emphasis on the role of the scientist, risk assessor, or other technical expert, other stakeholders can be involved in various ways, as agreed upon before the analysis phase begins. Some roles stakeholders might have in the analysis phase include (1) suggesting sources of data or providing data for the assessment; (2) helping clarify issues identified during problem formulation; (3) working alongside the risk assessment experts to see what data and assumptions are being used and why and to better understand how the risk assessment process works; and (4) suggesting alternate scenarios that may reflect more realistic exposure conditions in the community. A variety of roles for stakeholders in the analysis phase can be proposed and adapted for the particular circumstances of the individual case, assuming that the roles can be agreed upon by the team.

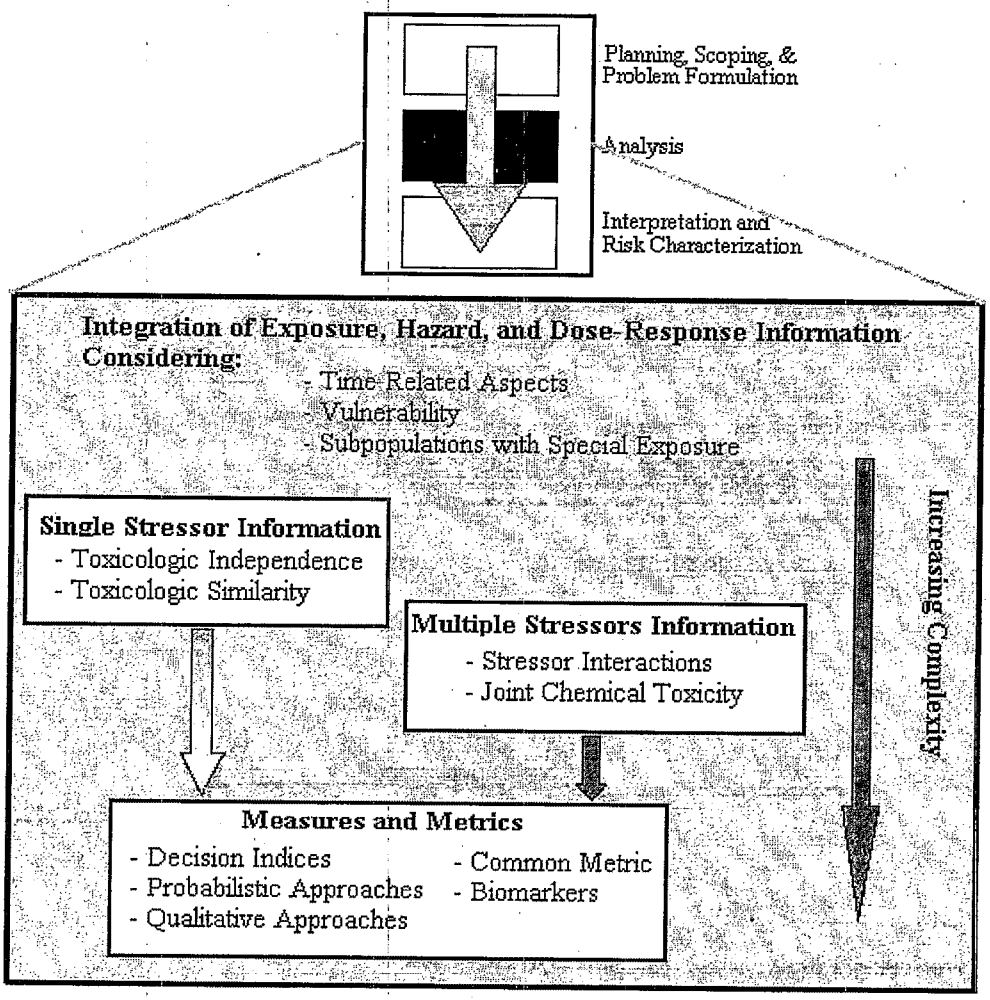


Figure 3-1. The Analysis phase.

information for these stressors and the method for combining the exposure information with the hazard and dose-response information to generate risk estimates or measures. As the risk analysis is refined, it may be appropriate to revisit and refine the exposure, hazard, and dose-response information in an iterative fashion.

In the integration of exposure, hazard, and dose-response information for a cumulative risk assessment, several aspects of the assessment may be particularly important. These include multiple-stressor hazard, dose-response and exposure issues, exposure time or duration-related issues, vulnerability (including susceptibility) of the study population along with the influencing factors (including life stage), and subpopulations with special exposures. These items are discussed in the following section along with the currently recognized methods for evaluating the toxicity or risk associated with mixtures.

The area of identifying and assessing risk to susceptible subpopulations has an increased profile in cumulative risk assessments. A variety of factors may be influential in affecting population susceptibility. The extent to which these can be considered will be heavily dependent on existing knowledge and available information.

Scope of EPA's National-Scale Assessment for Hazardous Air Pollutants (also see Figure 2-3):

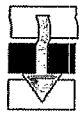
Stressors	33 priority urban hazardous air pollutants (HAPs)
Sources	Major industrial, small "area," mobile (on- and off-road), and extrinsic "background" in air
Pathways/media	Outdoor air, indoor air Microenvironments
Routes	Inhalation
Subpopulations	General population only
Endpoints	Cancers, developmental, central nervous system, kidney, liver, respiratory effects
Metrics	For cancer: distribution of high-end cancer risk estimates, predicted percent of population within predicted cancer risk ranges, predicted number of cancer cases, HAP-specific and cumulative For other effects: distribution of estimated hazard index values and estimated percent of population within specified ranges of index values

3.2. Available Methods and Approaches

Many aspects of traditional risk assessment methodology apply to cumulative risk assessment. Predicting cumulative risk of multiple stressors, however, has required the development of additional specific methods or approaches. Additionally, there are some aspects of risk assessment that, although common to both single-stressor and multiple-stressor assessments, may increase in complexity or significance in a cumulative risk assessment.

Although the aspects common to single-stressor and multiple-stressor assessments may be many (e.g., the added dimension of multiple stressors influences consideration of stressor sources, routes of exposure, environmental media/pathways, and other factors), several examples are cited here. As one example, the assessment of the dose-response relationship and the corresponding characterization of exposures in terms of duration, timing relevant to life stage, and exposure history gain an additional dimension with the need to consider them cumulatively in some way. The consideration of population susceptibility (as a part of vulnerability), as recommended by EPA (USEPA 1995a, b, 2000c), also increases in complexity. A third example of a complicating aspect in cumulative risk assessment is the consideration of subpopulations that have particularly distinctive exposures. These examples are further discussed in Section 3.2.1.

Although it is beyond the scope of this framework report to describe all risk methods in detail, Appendix B lists a variety of resources relevant to various exposure assessment methods. Relatively speaking, there is a great deal of information on assessing human and environmental exposures to chemical stressors and there is some information on biological and radiological stressors, but there is comparatively little information on many other types of stressors.



The most prominent aspect of cumulative risk assessment is often the prediction of the combined effects of multiple stressors. Past and current activities in the development of approaches for predicting risk of multiple stressors are described in USEPA (1986b, 2000e). Concepts, approaches, or methods described in these documents or elsewhere are discussed in section 3.2.2, with clarification of their applicability, limitations and notable points regarding interpretation of the results they produce.

3.2.1. Examples of Increased Complexity of Cumulative Risk Assessment

Cumulative risk assessments can be quite complex (see text box on the following page for an example). Three factors that can increase complexity in a cumulative risk assessment are (1) time-related aspects, (2) vulnerability (including susceptibility), and (3) subpopulations with special or particularly distinctive exposures. All three are relevant in single-stressor assessments, but they have the potential to be more complicated in multiple-stressor assessments

Time-related aspects. The issue of repeated exposures to a single stressor or exposures to multiple stressors that may vary in time dimensions may have implications for susceptibility, which, consequently, has implications for the dose-response relationship. Traditionally in dose-response assessment, there is an inherent presumption that, for many stressors and effects, it is the aggregate exposure (the combination of intensity and duration) to which the organism responds (e.g., Haber, 1924). Thus dose-response assessments based on one pattern of exposure (e.g., 6 hours per day, 5 days per week over a lifetime) are routinely applied to the assessment of risk associated with a variety of patterns of exposure.

In the case of linear carcinogens, this aggregate exposure assumption has been carried as an explicit assumption in the risk assessment step. Regardless of the details of the exposure circumstances in the study on which the cancer potency was based, it is assumed that there is a linear relationship between amounts of exposure and associated cancer risk. For nonlinear carcinogens[11], and conceivably for linear carcinogens, if data indicate deviation from the assumption that cancer risk is proportional to lifetime dose, the details and sequence of exposure may be important, both in developing the dose-response relationship and in predicting risk associated with exposures and life stages of interest.

Because some chemicals may have the ability to affect an organism's response to other chemicals, consideration of the time sequence of exposure may take on an additional layer of complexity in multiple-chemical cumulative risk assessments. For example, persons with relevant past exposures might have increased susceptibility to the effects of a particular chemical due to a previous exposure to the same—or a second—chemical.

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[11] The draft cancer guidelines (USEPA, 1999l) explicitly recognize the potential for nonlinear dose-response. It is only in the case where nonlinear response is modeled that time sequence of exposure can be considered in the risk assessment.

The National-Scale Air Toxics Assessment

The National Air Toxics Assessment (NATA), which is based on 1996 emissions data is an ongoing series of studies—some of which are completed—that will ultimately provide results that are useful in understanding the quality of air and its possible effect on human health nationwide. The assessment includes 32 air toxics (a subset of EPA's list of 188 air toxics) and also diesel particulate matter (which is used as a surrogate measure for diesel exhaust). Specifically, the assessment consists of four steps that will produce nationwide estimates of (1) the release of these pollutants into the air from various sources, (2) the concentration of these compounds in the air, (3) the exposure of populations to this air, and (4) the risk of both cancer and noncancer health effects resulting from this exposure.

Purpose: The results of the national-scale assessment will provide important information to help EPA continue to develop and implement various aspects of the national air toxics program. They will not be used directly to regulate sources of air toxics emissions. Although regulatory priority setting will be informed by this and future national assessments, risk-based regulations will be based on more refined and source-specific data and assessment tools. More specifically, the assessment results will help identify air toxics of greatest potential concern, characterize the relative contributions to air toxics concentrations and population exposures of different types of air toxics emissions sources (e.g., major, mobile), and set priorities for the collection of additional air toxics data and research to improve estimates of air toxics concentrations and their potential public health impacts. Important additional data collection activities will include upgrading emission inventory information, ambient air toxics monitoring, and information on adverse effects to health and the environment; establishing a baseline for tracking trends over time in modeled ambient concentrations of air toxics; and establishing a baseline for measuring progress toward meeting goals for inhalation risk reduction from ambient air toxics.

The Four Steps: The national-scale assessment includes the following four major steps for assessing air toxics across the contiguous United States (also Puerto Rico and the Virgin Islands).

(1) *Compiling a 1996 national emissions inventory of air toxics emissions from outdoor sources.* The types of emissions sources in the inventory include major stationary sources (e.g., large waste incinerators and factories), area and other sources (e.g., dry cleaners, small manufacturers, wildfires), and both onroad and nonroad mobile sources (e.g., cars, trucks, boats). EPA made some modifications to the 1996 National Toxics Inventory to prepare the emissions for computer modeling.

(2) *Estimating 1996 ambient concentrations based on the 1996 emissions as input to an air dispersion model (the ASPEN model).* As part of this modeling exercise, EPA compared estimated ambient concentrations to available ambient air toxics monitoring data to evaluate model performance.

(3) *Estimating 1996 population exposures based on a screening-level inhalation exposure model (HAPEM4) and the estimated ambient concentrations (from the ASPEN model) as input to the exposure model.* Estimating exposure is a key step in determining potential health risk. People move around from one location to another, outside to inside, etc., so exposure is not the same as concentration at a static site. People also breathe at different rates depending on their activity levels, so the amount of air they take in varies. For these reasons, the average concentration of a pollutant that people breathe (i.e., exposure concentration) may be significantly higher or lower than the concentration at a fixed location (i.e., ambient concentration).

(4) *Characterizing 1996 potential public health risks due to inhalation of air toxics.* This includes both cancer and noncancer effects using available information on air toxics health effects, current EPA risk assessment and risk characterization guidelines, and estimated population exposures. Using the toxicological independence formula and the default assumption of additivity of risks (USEPA, 1986b, 2000e), this assessment combines cancer risk estimates by summing them for certain weight-of-evidence groupings and also across all groupings. For noncancer effects, the assessment assumes dose additivity and aggregates or sums hazard quotients for individual air toxics that affect the same organ or organ system (USEPA, 2000e), in this case combining air toxics that act as respiratory irritants.

These considerations suggest that for cumulative risk assessment, chemical exposures need to be characterized in terms of which other chemicals are present, and when. As noted in ILSI (1999), "Data collected specifically to support a cumulative exposure assessment should conserve the covariance and dependency structures associated with the chemicals of concern." It is important to note, however, that the level of detail to which exposures are characterized should be closely tied to the level of detail of information available in the dose-response assessment, because a lack of corresponding detail in the dose-response assessment can pose a limitation on the interpretation and usefulness of detailed exposure estimates.

Cumulative risk assessment can present challenges in matching exposure estimates with dose-response relationships. Ideally, the dose-response assessment will indicate whether the time sequence for the chemical(s) or stressors of interest in the assessment is important for risk estimation. In cumulative assessments involving chemicals for which the time sequence of exposure is important, it may be necessary to characterize the details and sequence of exposure to the exposed population (see text box on the following page), so that there will be a match in not only the form, but also in the assumptions between the dose-response relationship and the exposure/dose estimate.

Vulnerability. One of the concepts that can be used in risk assessments (both for human health and ecological assessments) is that of *vulnerability* of the population or ecosystem. Vulnerability has been a common topic in socioeconomic and environmental studies. The European Commission's TEMRAP (The European Multi-Hazard Risk Assessment Project), studying vulnerability to natural disasters such as floods, windstorms, fires, earthquakes, and others, defines vulnerability as "the intrinsic predisposition of an exposed element [organism, population, or ecologically valuable entity] to be at risk of suffering losses (life, health, cultural or economic) upon the occurrence of an event of [a specific] intensity" (European Commission, 2000). Kasperson et al. (1995) defines vulnerability as "The propensity of social or ecological systems to suffer harm from external stresses and perturbations. Involves the sensitivity to exposures and adaptive measures to anticipate and reduce future harm." Kasperson (2000) identified four types of vulnerability, discussed further below.

The Agency's risk characterization policy and guidance (USEPA, 2000c) touches on this concept by recommending that risk assessments "address or provide descriptions of [risk to]...important subgroups of the population, such as highly exposed or highly susceptible groups." Further, the Agency's guidance on planning and scoping for cumulative risk assessments (USEPA, 1995b) recognizes the importance of "defining the characteristics of the population at risk, which include individuals or sensitive subgroups...." That guidance also recognizes the potential importance of other social, economic, behavioral, or psychological stressors that may contribute to adverse health effects (e.g., existing health condition, anxiety, nutritional status, crime, and congestion). As discussed below, the ways in which the Agency and others describe these concepts in the context of human health risk assessment overlap the various ways described by Kasperson (2000) in which human and biological ecosystems, communities, and populations may be vulnerable: susceptibility/sensitivity, differential exposure, differential preparedness, and differential ability to recover.

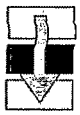
Examples of Exposure Models that Consider Time Aspects

Calendex (Novigen Sciences, Inc) integrates different pathways (e.g., dietary [food and water] and residential) and routes of exposure (oral, dermal, inhalation) using a calendar-based probabilistic approach. One of the important factors of this approach is that it provides estimates of risk that reflect aggregate and cumulative exposure to discrete individuals, with exposure pathways and routes appropriately linked for the scenarios being assessed. Calendex also allows one to estimate exposure before and after the use of a chemical, as well as during degradation periods. Calendar-based assessments maintain the integrity of the individual by capturing the location of the exposed individual, the time of year in which he or she was exposed, and the patterns of exposure. Calendex also allows for a variety of time-breakout options for the analysis of exposure.

APEX - The Air Pollution Exposure (APEX) model is based on the probabilistic National Ambient Air Quality Standards exposure model (pNEM) for carbon monoxide (Johnson et al., 2000). This model mimics the basic abilities of the pNEM/CO model; it calculates the distributions of human exposure to selected airborne pollutants within a selected study area as a function of time. As a dose model (for carbon monoxide), it calculates the pollutant dose within the body, specifically summarized by the blood carboxyhemoglobin (COHb) concentration. APEX is a *cohort-microenvironment* exposure model in that it combines daily activity diaries to form a composite year-long activity pattern that represents specific *population cohorts* as they move from one *microenvironment* to another. A *cohort* consists of a subset of the population that is expected to have somewhat similar activity (and hence exposure) patterns; it is formed by combining demographic groups and geographic locations (districts). Once each cohort has been modeled and its relative size determined, an exposure distribution for the entire population can be assembled. A *microenvironment* is a description of the immediate surroundings of an individual that serves as an indicator of exposure (e.g., inside a residence, school, or car; outdoors; etc.). APEX has been developed as one of the inhalation exposure models accessible in the Exposure Event Module of the Total Risk Integrated Methodology (TRIM.Expo) for assessment of exposures to either criteria or hazardous air pollutants (USEPA, 1999j)

Other models include **LifeLine**, developed under a cooperative agreement between EPA/OPP and Hampshire Research Institute (HRI, 1999, 2000); **Stochastic Human Exposure and Dose Simulation** (SHEDS), under development by EPA's Office of Research and Development (Zartarian et al., 2000), and **Cumulative and Aggregate Risk Evaluation System** (CARES), under development by member companies of the American Crop Protection Association (ACPA, 1999) along with **Residential Exposure Year** (RExY), which is being developed by Infoscientific.com.

The first of Kasperson's categories is *susceptibility* or *sensitivity*. Although these two words may have slightly different meanings, they are often used interchangeably. They refer to an increased likelihood of sustaining an adverse effect, and they are often discussed in terms of relationship to a factor describing a human subpopulation. For example, susceptible persons or populations may be those who are significantly more liable than the general population to be affected by a stressor due to life stage (e.g., children, the elderly, or pregnant women), genetic polymorphisms (e.g., the small but significant percentage of the population who have genetic susceptibilities), prior immune reactions (e.g., individuals who have been "sensitized" to a particular chemical), disease state (e.g., asthmatics), or prior damage to cells or systems (e.g., individuals with damaged ear structures due to prior exposure to toluene, making them more sensitive to damage by high noise levels) (Morata et al., 1997). Confronted with equal concentrations of a chemical for equal durations, for example, a biologically susceptible or



sensitive individual may show effects, whereas the typical individual within the population would have no or less severe effects. This category would also include generation-skipping effects. Although we generally do not have a lot of data available on this topic, susceptibilities or sensitivities may also exist among races or genders.

Kasperson's second category of vulnerability is *differential exposure*. Although it is obvious from examining a dose-response curve that two individuals at different exposure levels may have a different likelihood of effects, this category extends to differences in historical exposure, body burden, and background exposure, which are sometimes overlooked in an assessment. When looking at the dose-response curves for a typical individual and an individual vulnerable due to differential exposure, the curves may be the same, but the vulnerable individual may be currently at a higher dose due to greater current or prior exposure and body burden, so an increment of additional exposure may (due to slope of the curve at that point) produce a more pronounced effect than in a typical individual.

Kasperson's third category of vulnerability is *differential preparedness* to withstand the insult of the stressor. This is linked to what kind of coping systems and resources an individual, population, or community has: the more prepared, the less vulnerable. As an example, consider two individuals, one of whom has had a childhood disease immunization shot and the other has not. The two may be exposed to the same insult, but due to a difference in preparedness, the effects on the person with the immunization shot may be much milder or nonexistent. As another example, hurricanes typically cause less damage to boarded up homes than they do to homes without this reinforcement, even though the weather insult to both homes may be the same.

Kasperson's fourth category is the *differential ability to recover* from the effects of the stressor. This again is linked to what kind of coping systems and resources an individual, population, or community has. One aspect of differential ability to recover is illustrated by differing survival rates for the same disease (e.g., Lantz et al., 1998). Put in terms of progression of disease, for example, two persons in an early stage of cancer have different prospects for recovery if one is treated immediately while the other does not have access to, or does not trust, health care. On the ecological side, opportunistic infections in marine mammals[12] appear to be related to accumulation of polychlorinated biphenyls and organotin compounds, which cause an immunosuppression response in laboratory animals (Tanabe, 1998).

Preparedness and ability to recover are often crucial factors in ecological assessments. In human health assessments, lack of access to health care, income differences, unemployment, or lack of insurance, for example, may affect a community's ability to prepare for or recover from a stressor.

Cumulative risk assessments may be uniquely suited to addressing the issues related to vulnerability. In order to do so, however, there should be some relationship between the factors

[12] That is, infections easily warded off by healthy marine mammals.

discussed above and changes in risk. Many of these factors have not yet been extensively developed beyond correlations between mortality rates and several socioeconomic factors, such as income (e.g., Lynch et al., 1998). Susceptibility has been more developed than the other factors, and current approaches implemented by EPA and others to address risk of noncancer endpoints routinely employ a 10-fold factor to address heterogeneity in sensitivity. Variability with regard to susceptibility is discussed in detail by NRC (1994), and the current state of knowledge concerning epidemiologically based (e.g., oncogene-specific) risk factors provides empirical data upon which at least crude estimates of the magnitude of heterogeneity in susceptibility to toxic response can be based. However, much research in this area remains to be done.

Subpopulations with Special Exposures. Certain subpopulations can be highly exposed to stressors because of geographic proximity to the sources of these stressors, coincident direct or indirect occupational exposures, activity patterns, or a combination of these factors. The Agency's risk characterization policy and guidance (USEPA, 2000c) includes recognition of the need for risk information to include, as available, information on highly exposed subgroups. Accordingly, risk assessments, including cumulative assessments, may need to put special emphasis on identifying and evaluating these subpopulations.

Subpopulations at risk of high exposure due to geographic proximity could include workers at a facility that is a source of a stressor or residents near such sources. Specific examples might be people living downwind from a coal-burning power plant, those near and using a polluted water body (e.g., for fishing or recreation), or those living or working near roadways with high levels of vehicular traffic. Occupational exposures may be either direct (occurring in the workplace) or indirect (occurring at home). Indirect occupational exposures include those experienced by family members who may be exposed to occupational chemicals brought into the house by the worker (e.g., on clothing). Thus, workers or family members may be subject to greater exposures than others in the population who do not have this additional burden.

Examples of subpopulations at high exposure due to activity patterns may include people who exercise heavily in polluted air, recreational or subsistence fishers or hunters who consume large quantities of fish or game, farmers or others who get a large proportion of their food from a location near a source of pollution and live in areas with high pesticide use, individuals who have long commutes in automobiles, or children (because they consume a larger amount of food, drink, and air relative to their body weight and because of additional exposure routes such as incidental soil ingestion). Additionally, some subpopulations may be affected by the combined impact of high geographic exposure and high-exposure activity patterns (e.g., runners who run along heavily traveled roadways and people who fish for food in heavily polluted urban rivers).

It is important to recognize that some heavily exposed populations may also be particularly vulnerable or susceptible to the effects associated with the stressors of concern. Examples of those who could be particularly vulnerable to certain stressors include children during certain stages of development, people with chronic respiratory problems, the elderly, and those who are economically disadvantaged and do not have access to medical care. A

cumulative risk assessment may need to take into account potential combinations of high exposure and high vulnerability, but few, if any, methods are currently available and accepted to address the combined effects of exposure and vulnerability. This is an important area for further research and methods development.

3.2.2. Approaches for Predicting Risk of Multiple Stressors

Combination toxicology (Carpy et al., 2000) is the study of the toxicity of mixtures. In such studies, one may either measure the mixture toxicity directly (whole mixture toxicity), or one may develop an estimate of the combined toxicity from information on the multiple component stressors acting in concert with each other. (Toxicity of chemical mixtures has also been modeled on a physiologically based pharmacokinetic basis [e.g., Haddad et al., 2000, 2001].) If evaluated using its component chemicals, the mixture toxicity data set should be treated only as a snapshot of a multidimensional dose-response relationship, because the joint toxicity and interactions can change with changes in exposure route, duration, relative proportions of the components, or the effect being tracked. The application of such a data set to a specific situation then requires careful matching of the test mixture composition and exposure conditions to those of the target situation. In whole mixture toxicity, once the mixture toxicity is known, a risk evaluation can be done on the mixture using the 1983 NRC risk assessment paradigm. On the other hand, component-based mixture assessments are rarely evaluated using the strict NRC paradigm, because the exposure and toxicity information should be compatible, requiring some iteration to obtain toxicity information that is relevant to the actual exposure estimates (USEPA, 2000e).

To address concerns over health risks from multichemical exposures, EPA issued guidelines for health risk from exposure to chemical mixtures in 1986 (USEPA, 1986b). The guidelines described broad concepts related to mixtures exposure and toxicity and included few specific procedures. In 1989, EPA published guidance for the Superfund program on hazardous waste that gave practical steps for conducting a mixtures risk assessment (USEPA, 1989a). Also in 1989, EPA published the revised document on the use of TEFs for characterizing health risks of the class of toxicologically similar chemicals that included the dibenzodioxins and dibenzofurans (USEPA, 1989b). In 1990, EPA published a technical support document to provide more detailed information on toxicity of whole mixtures and on toxicologic interactions (e.g., synergism) between chemicals in a two-chemical mixture (USEPA, 1990a). Whole-mixture assessments, toxicologic independence and similarity, and risk methods using toxicologic interactions are discussed at length in USEPA (2000e).

Risk assessment for mixtures usually involves substantial uncertainty. If the mixture is treated as a single complex substance, these uncertainties range from inexact descriptions of exposure to inadequate toxicity information. When viewed as a collection of a few component chemicals, the uncertainties also include the generally poor understanding of the magnitude and

nature of toxicologic interactions, especially those involving three or more chemicals. Because of these uncertainties, the assessment of health risk from chemical mixtures should include a thorough discussion of all assumptions and the identification, when possible, of the major sources of uncertainty.

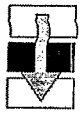
3.2.2.1. Single stressor information

Assessments that evaluate the risk from a single stressor do not fall into the category of cumulative risk assessments under the definition given in Section 1.3, whether these single-stressor assessments address a single (dominant) endpoint or multiple endpoints or whether the exposures are simple or complex (e.g., multisource, multipathway, multiroute exposure). Some may be termed "aggregate risk assessments" by extension of the FQPA terminology. They can, however, provide useful information for cumulative assessments.

A cumulative risk assessment considers the joint impact of multiple stressors. Studies on individual stressors can, however, provide informative qualitative information for multistressor assessments, particularly regarding hazard identification. The collection of single-stressor effects can indicate the variety of types of adverse effects likely to result from the stressor combination, although perhaps not the magnitude or extent of the effects. Factors affecting population susceptibility to the individual chemicals are also likely to be important with the combined exposure. To go further in terms of quantitative risk assessment requires consideration of the potential for joint toxicity. For most exposure situations, hazard and dose-response studies of all of the joint effects from the multiple stressors will not be available, so that conclusions will have to be based at least partly on the single stressor information.

Exposure assessments for single stressors also need further consideration before they can be used to characterize long-term exposure to all the stressors by all pathways. Transport and environmental transformation of a chemical can be influenced by the presence of other chemicals. Consequently, both the exposure levels and the relative proportions of chemicals at future times may not correspond well to present measurements of a combination of chemicals unless these influences are taken into account. In addition, exposure to one stressor may influence the uptake of a second stressor. For example, a nonchemical stressor that increases ventilation rate will increase the inhalation uptake of airborne chemicals.

Toxicologic independence. Two situations allow plausible approximations of the joint exposure-response relationship using only the single stressor information: toxicologic independence and toxicologic similarity (USEPA, 2000e). In the case of toxicologic independence, if the toxicity modes of action are biologically independent, then as long as there are no pre-toxicity interactions (e.g., metabolic inhibition, influence on uptake), the single stressor information is sufficient to approximate the joint exposure-response relationship. When the effects from two or more stressors are different, the cumulative response, if toxicologically independent, is merely all the single-stressor responses, as if the other stressors were not present. For example, joint but low exposure to heat (causing minor elevated heart rate and toluene (causing minor hearing loss) would be expected to cause both the minor heart rate elevation and minor hearing loss, but to the same extent as expected for each stressor alone. If each stressor is



below its toxicity threshold, then for stressors exhibiting toxicologic independence, there will be no estimated cumulative response, because the set of individual responses is then a collection of zeros.

When the single stressor and cumulative toxicities are each represented by a frequency or probability for affected individuals—also termed a probabilistic risk—then independence means that "response addition," as defined in USEPA (2000e), can be applied for each adverse effect that the stressors have in common. When all the single-stressor risks are low, the joint risk of a common effect under response addition can be approximated by the simple sum of the single-stressor risks. For example, if reproductive toxicity is the general effect common to the multiple chemicals, the cumulative risk of reproductive effects (at low single-chemical risk levels) is approximately the sum of the single-chemical reproductive risks. Risk addition under independence places no constraints on the individual chemical dose-response curves.

Toxicologic Similarity. In the second situation, the stressors are grouped according to the common mode of action for each effect of concern determined in the planning and scoping phase (USEPA, 2002a). For all effects caused by that mode of action, "dose addition" (USEPA, 2000e) can be applied to the stressor group. Thus far, this approach has been used only with combinations of toxicologically similar chemicals, not with combinations of chemicals with other kinds of stressors such as radiation, physical factors, or health status. With similar chemicals, each chemical exposure is converted into the equivalent exposure level of one of the chemicals, called the index chemical. The joint toxicity or risk from the combined exposure is then estimated by determining the effects or risk for that equivalent exposure level using the dose-response information for the index chemical. For example, with the dioxins and furans (see text box on next page), each congener exposure level is converted into its equivalent exposure as the index chemical, 2,3,7,8-TCDD (USEPA, 1989b).

Although the assumption itself is not complicated, the decision to assume toxicologic similarity can be complicated, depending on the level of assessment decided on in the planning and scoping phase and described in the analysis plan. The implementation used in Superfund assessments (USEPA, 1989a, Part D) is a rough approximation to dose addition where a hazardindex is determined whenever chemicals have a common target organ. The implementation by the Office of Pesticide Programs in support of FQPA (USEPA, 2002a) is much more extensive and requires knowledge of modes of action in order to calculate the Relative Potency Factors (RPFs) for the effect of concern (see example in Appendix E). The TEF method used for the dioxins is a special case of the RPF method (see Appendix E); it requires the most toxicologic similarity because the similarity applies to every toxic effect by any type of exposure (USEPA, 2000e).

Single stressor information can also be used with dissimilar chemicals to gauge the potential for toxicologic interaction. For example, chemicals with long whole-body half-lives or long tissue residence times have the potential to be present in those tissues at the same time. Such overlapping exposures can result in a higher effective tissue dose, altered tissue doses caused by toxicokinetic interactions, or altered toxicity from interacting toxic mechanisms.

Toxicologic Similarity: The Dioxin Reassessment

Scientists from EPA, other Federal agencies, and the general scientific community have been involved in a comprehensive reassessment of dioxin exposure and human health effects since 1991 (USEPA, 2002d). The final dioxin reassessment will consist of three parts. *Part 1: Estimating Exposure to Dioxin-Like Compounds* will include four volumes that focus on sources, levels of dioxin-like compounds in environmental media, and human exposures. *Part 2: Human Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* will consist of two volumes that include information on critical human health endpoints, mode of action, pharmacokinetics, dose-response, and toxicity equivalence factors (TEFs) *Part 3: Integrated Summary and Risk Characterization for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* will be a stand-alone document. In this summary and characterization, key findings pertinent to understanding the potential hazards and risks of dioxins are described and integrated, including a discussion of all important assumptions and uncertainties.

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is highly toxic to many animal species, producing a variety of cancer and noncancer effects. Other 2,3,7,8-substituted polychlorinated dibenzo-*p*-dioxins (PCDDs) and dibenzofurans (PCDFs) and coplanar polychlorinated biphenyls (PCBs) exhibit similar effects, albeit at different doses and with different degrees of confidence in the database. The similarities in toxicity between species and across different dioxin congeners stem from a common mode of action via initial binding to the aryl hydrocarbon (Ah) receptor. This common mode of action is supported by consistency in effects evident from data from multiple congeners. This has led to an international scientific consensus that it is prudent science policy to use the concept of TEFs to sum the contributions of individual PCDD, PCDF, and coplanar PCB congeners with dioxin-like activity (van den Berg et al., 1998). The data supportive of dioxin-like toxicity, both cancer and noncancer, are strongest for those congeners that are the major contributors to the risk to human populations. In addressing receptor-mediated responses resulting from complex mixtures of dioxin-like congeners, this assessment has provided a basis for the use of integrated measures of dose, such as average body burden, as more appropriate default metrics than daily intake. The Agency recognizes, however, that the final choice of an appropriate dose metric may depend on the endpoint under evaluation.

In this study, 2,3,7,8-TCDD was chosen as the index chemical, and the other dibenzo-*p*-dioxins and dibenzofurans and coplanar PCB doses were adjusted to 2,3,7,8-TCDD-equivalent toxicities so the doses could be added.

When a careful evaluation indicates no internal dose overlap, including metabolites, the single exposures might be considered independently.

3.2.2.2. Information on stressor interactions and multiple exposures

One important simplification that is common in single-stressor human health assessments is the separate evaluation of many of the key steps. That is, simplifying assumptions have often been made regarding many characteristics of exposure (e.g., continuous vs. intermittent variations in magnitude). For a given exposure route, for example, only one dose-response curve may be used for the bounding case of setting a cleanup or action level of exposure and also the predictive case of estimating existing risk. These simplifying assumptions allow the dose-response step to be performed in isolation from the exposure assessment step, with the two steps executed in either order. For health-protective action levels, one may use bounds, such as the upper bounds on toxic potency and exposure and lower bounds on the resulting acceptable

exposure level. Such bounds may be much easier to calculate, but they may be more difficult to interpret in terms of the uncertainties, likelihood, and closeness to the best or central estimate.

The incorporation of multiple chemicals, other stressors, and multiple exposure conditions obviously complicates the assessment and the use of simplifying assumptions.[13] In cumulative assessments, performing the exposure and dose-response steps of the risk assessment paradigm separately is an approximation that obviously invokes a simplifying assumption. If the dose-response data do not represent the same conditions as the exposure being assessed, an extrapolation has to be made, which introduces additional uncertainty that should be clearly stated. Joint or cumulative toxicity depends on the total dose or exposure, relative exposure levels, and the many characteristics of exposure (e.g., duration, continuous vs. intermittent presence, route, co-occurrence with other chemicals). In many cases, the complexities introduced by multiple stressors will not allow use of some of the common simplifying assumptions of single-stressor assessments. For example, toxicologic interactions have been shown to change when the same doses are used but the sequence of exposure is reversed (i.e., chemical B then A instead of A then B), so that the exposure and dose-response analysis should be compatible and performed together.

Nonchemical stressors (e.g., biological entities or even physical stressors such as noise) can also interact with chemicals to change the risks either that would cause separately. For example, chemicals such as toluene can damage the auditory system and have been shown to potentiate the effects of a physical stressor, noise, on hearing loss (Morata et al., 1997; Morata, 2000). For aquatic organisms, the toxicity of polyaromatic hydrocarbons increased with exposure to ultraviolet radiation (Oris and Geisy, 1985).

Toxicity and interaction data that cover the full range of exposures for the exposure-response relationship for the mixture of interest is usually impossible to obtain because of limits on budget and other resources. More feasible approaches to cumulative risk characterization, beyond that with various simplifying assumptions, then require close matching of the exposure and dose-response steps to minimize the data requirements. In many cases, screening-level ranking may be the only practical assessment. In some cases there will be sufficient information for some quantitative evaluation of cumulative health risks that reflect both the complex exposures and toxicologic interactions.

"Joint chemical toxicity" means the outcome of exposure to multiple chemicals that includes the single-chemical effects along with any toxicologic interactions. Chemical interactions can be divided into two major categories: those resulting from a toxicokinetic mode of action and those resulting from a toxicodynamic mode of action (USEPA, 2000e). Toxicokinetic modes of interaction involve alterations in metabolism or disposition of the toxic chemicals, for example, by the induction or inhibition of enzymes involved in xenobiotic activation and detoxification. Toxicodynamic modes of interaction include those processes that

[13] For ecological risk assessments, Gentile et al. (1999) review the theory and several methods for evaluating stressor/response linkages and stressor interactions for multiple stressors.

affect a tissue's response or susceptibility to toxic injury. A simplifying observation is that most interactions seem to involve pharmacokinetics. Unfortunately, most studies of toxicologic interaction to date have involved only two chemicals, and few have quantified the magnitude of the interaction or its dependence on exposure conditions.

Toxicologic interactions are commonly described in terms of *synergism* or *antagonism*. These terms are only marginally useful, in part because the underlying toxicologic concepts are only defined for two-chemical mixtures, and most environmental and occupational exposures are to mixtures of many more chemicals. Further, the mathematical characterizations of synergism and antagonism are inextricably linked to the prevailing definition of "no interaction," instead of to some intrinsic toxicologic property (Hertzberg and MacDonell, 2002). EPA (USEPA, 2000e) has selected "dose addition" as the primary "no interaction" definition for mixture risk assessment, so that synergism would represent observed toxic effects that exceed those predicted from dose addition . The EPA mixture risk guidance also describes a modified hazard index that incorporates evidence of pairwise toxicologic interactions but notes that the pairwise evidence may be specific to the exposure conditions of the study. The guidance further encourages development of full biomathematical models for the joint toxicity—such as those based on pharmacokinetics—so that qualitative interaction labels such as synergism are replaced by quantitative estimates of mixture response that directly reflect the actual environmental exposure levels.

3.2.2.3. Decision indices

Among the complexities of cumulative risk assessments is the frequent need to combine widely differing types of data. Exposure data for some stressors may be available only as time-weighted averages, whereas other data reflect daily human activity patterns. Toxicity data for some chemicals may allow estimation of probabilistic risk for one endpoint while providing only qualitative descriptions of other endpoints. It is possible to develop the risk characterization using the original information in a matrix, but such a summary will be difficult to evaluate and communicate. One approach to diverse multivariate data that has been used successfully for weather forecasting is the decision index, with examples such as the smog index, the pollen count, and the mold index commonly used to assist in public and personal decisions about environmental exposure. A similar approach can be taken for cumulative risk assessment (Hertzberg, 2000).

The advantage of a decision index is the simplicity in converting highly multivariate technical information into a single number. The most common example used for cumulative health risk is the hazard index for mixture risk (see box on next page). Although specific for a single affected target organ, each hazard index reflects multiple studies of multiple chemicals, often involving multiple test animal species and test exposures and highly varied measures of toxicity.

The main disadvantage of a simple index is that the uncertainties in its calculation are largely hidden. Another key disadvantage is in quantifying what are often scientific judgments. For example, the hazard index implemented under Superfund (USEPA, 1989a) is a number whose decision threshold is usually given as 1.0, so that when the hazard index is greater than 1, additional action is indicated. The actual value of a hazard index is not that informative: a value of 6 is not necessarily twice as bad as a value of 3. This is partly due to the uncertainty factors necessary to develop the reference dose (RfD) or the reference concentration (RfC). The total value of these factors can be as low as 3 or as high as 3000, depending on the data upon which the RfD or RfC for a specific chemical is based (Barnes et al., 1988; Beck et al., 1993; USEPA, 1994; Dourson et al., 1996; USEPA, 2002e).

The Hazard Index

The hazard index (HI) for oral exposure is implemented by Superfund assessors by the formula:

$$HI = \text{sum}[\, HQ_j \,] = \text{sum}[\, E_j/RfD_j \,]$$

where E_j and RfD_j are the daily exposure and reference dose of chemical j.

The RfD is itself a kind of decision index in that it reflects a dose that is selected to be sufficiently low that any toxic effects are judged highly unlikely. All available dose-response data on all effects are considered in determining each RfD. Uncertainties in the RfD will differ across the chemicals, making the uncertainty in HI difficult to characterize.

One alternative for addressing multiple effects is to recast these qualitative judgments in terms of severity categories or levels of concern (e.g., high/medium/low) and then use statistical methods such as categorical regression that use only the ordering of the severity scores but not their actual values. The result is not a risk of a particular toxic effect but rather a risk of exceeding a certain minimum toxic severity level or level of minimal concern (Hertzberg, 1989; Guth et al., 1993). In the best situations, such as the EPA interaction-based hazard index (USEPA, 2000e), the decision index formula is modular, so component pieces can be evaluated separately for accuracy and improvements in one area can be easily incorporated to give an improved index.

Another example of a decision index with more overt display of its diverse parts is the Hazard Ranking System (HRS) (47 *Fed. Reg.* 31219, dated July 16, 1982, and amended 55 *Fed. Reg.* 51532, dated December 14, 1990), a formula developed for characterizing the relative hazards of a particular waste site. These hazards were highly diverse and include corrosivity, explosivity, toxicity, and soil conditions. As with the hazard index, different uncertainties in the components make the uncertainty of the HRS index difficult to describe. Instead of merely presenting the index as a number, a graphical presentation such as the star plots of multivariate data could be used (Chambers et al., 1983; Hertzberg, 2000), where each arm of the star represents one of the sub-indices. Although this approach shows the relative contribution of each factor, it again hides the uncertainties of the factors as well as of the HRS index itself.

Hybrid methods that combine judgment with numerical descriptions of risk or dose-response have also been used for complex risk assessments. The EPA interaction-based hazard index (USEPA, 2000e) and the mixture risk approaches of the Agency for Toxic Substances and Disease Registry (ATSDR) (Hansen, et al., 1998) both include a judgmental weight-of-evidence

(WOE) score to reflect the strength of evidence for toxicologic interactions and relevance to human health risk. The ATSDR WOE is used in communicating risks and intervention options, whereas the EPA WOE is used to calculate a modified hazard index. A slightly different approach is the Integral Search System database program for combinations of carcinogens (Woo et al., 1994) by which available studies on pairwise interactions of carcinogenicity are used to modify the risk range of the combination from that predicted by response addition (USEPA, 2000e). In all these cases, scientific judgment is used to alter the risk description or quantitative estimate, but only in terms of an approximate risk interval or a decision threshold.

3.2.2.4. Probabilistic approaches

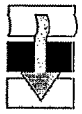
The recent report by Bogen (2001) illustrates an alternative probabilistic approach to noncancer endpoints in which methods used for integrated quantitative treatment of uncertainty and variability are made consistent with those used for probabilistic assessment of cancer risk. This report addresses many issues concerning the implementation of probabilistic methods for noncancer endpoints and cites a number of related references (e.g., Lewis, 1993; Dourson et al., 1997; Slob and Pieters, 1998).

Any approach to cumulative risk assessment should carefully define the set of relevant endpoints. Precisely how this is done has important logical and practical implications for how the cumulative risk may be calculated and interpreted. For example, the risk of inducing a given endpoint may differ among different people in a population at risk for some endpoints, (e.g., cancer conditional on all carcinogen exposures) but may be unaffected by interindividual variability (e.g., in exposure or susceptibility) for other endpoints (such as ecological or aesthetic effects). Defining the latter risks in terms of individual risk per se will thus complicate calculating cumulative risk if a probabilistic approach to cumulative risk assessment is used and perhaps if other approaches are used as well.

In contrast, the probabilistic approach to cumulative risk assessment may be facilitated by defining the risk of a given endpoint in terms of *population risk*, that is, in terms of the predicted number of cases of that endpoint. Alternatively (or additionally), similar simplification can be achieved for all heterogeneous endpoints by defining the risk only with respect to those persons in the population at risk who are reasonably maximally exposed (e.g., individuals adjacent to a proposed source) or to those persons who will incur the greatest increased risk (e.g., persons at a vulnerable life stage, such as children, or other members of a sensitive subpopulation who might be located adjacent to a proposed source).

3.3. Areas of Complexity and Current Research

One reason for the somewhat limited availability of cumulative risk assessments may be the accompanying complexity that arises in various aspects of the assessment. Some of this complexity is discussed in the previous section, along with currently available methods specific to human health risk assessment. In this section, some areas where research is ongoing are discussed, and some existing methods for quantitatively assessing multiple types of risk or hazard using a single metric are described.



3.3.1. Interactions Between Stressors and Other Factors

In identifying and characterizing susceptible subpopulations, it may be important to consider a variety of factors, such as current physical and mental health status and past exposure histories, that may exacerbate the effects of the stressors of interest. Social factors such as community property values, source of income, level of income, and standard of living may also affect vulnerability of subpopulations to certain other stressors. Risks associated with chemical or biological stressors may be significantly affected by "vulnerability factors" such as lack of health care or genetic predisposition to some diseases and effects. Community traditions and beliefs may affect activity patterns and behaviors and therefore affect exposure to stressors as well as the acceptability of the risk management options. Depending on the scope of the assessment and the stressors included, lifestyle factors such as smoking and nutritional habits, among others, may be important to susceptibility.

In what could be characterized as an exploration of how somewhat abstract factors may affect susceptibility, ATSDR held an expert panel workshop on the subject of psychological responses to hazardous substances (ATSDR, 1995). In its report, the panel noted that there is "a significant lack of information" about how often communities near hazardous waste sites or spills suffer chronic stress reactions, but that psychological stress causes both psychological changes that can be measured by self-reports and objective tests as well as physical changes such as increased blood pressure and heart rate and biochemical parameters such as changes in stress hormones. Assessing the levels of stress and their potential contribution to risk is difficult for a variety of reasons. The report notes that

> unlike the damage and injuries caused by a natural disaster, many toxic substances are invisible to the senses.... In the face of no external cues and uncertain circumstances, each person affected by a hazardous exposure develops their own beliefs about the nature of the resultant harm. These beliefs are based on the facts available to them, pre-existing opinions, cultural factors, sensory cues, and the beliefs of leaders and others in the community.... Unlike a natural disaster, which hits and has a low point after which recovery can begin, the response to a hazardous waste site can take 12 to 20 years.

Although the ATSDR report indicates that stress related to hazardous chemicals in the community can show measurable physical effects, it stopped short of saying that long-term health effects from this stress can be converted to risk estimates at this time. One of the questions the panel was asked to address was, "Given what is known regarding the psychology of stress, are there interactions between chronic stress and exposure to neurotoxicants that could shift the dose-response curve for neurotoxins?" The panel concluded:

> A methodology does not exist that would allow for discrimination between stress or neurotoxicant-mediated effects in community-based studies.... Experimental animal data exist to suggest that stress levels can modulate a toxic response; however, the question of specificity remains. Given that stress can induce or unmask a latent effect of a toxicant, there is the possibility that chronic stress

could alter basal levels of neurofunctioning and shift the threshold for neurotoxicity. Indeed, one may find a shift in the dose response to a neurotoxicant; however, a specific effect of the neurotoxicant should be examined in greater detail than the generalized non-specific endpoints. Detecting such a shift would require the knowledge of toxicant-specific biological mechanisms of actions, which most often are not known.

The ATSDR report contains many suggestions for research to fill data gaps in this area, and scientists may make significant progress in the coming years.

"Quality-of-life" issues may also influence risk to health or the environment, and evaluating those issues may require an approach that differs from the traditional NRC risk paradigm. Although a cumulative human health or ecological health risk assessment is not a cumulative impact analysis such as is conducted under NEPA, changes in quality-of-life factors may affect the vulnerability of a population to health or ecological risks and consequently may be part of the considerations in a cumulative risk assessment. Because few, if any, established and accepted relationships are currently available to quantitatively link quality-of-life factors and health or ecological risk, this further research in this area may prove valuable.

To evaluate the effects on human or ecological health from these types of stressors, a more deliberative approach (in the analytical-deliberative process) is needed than is used in, say, cancer risk analysis. EPA (USEPA, 1993b) suggests a six-step process that may help characterize quality-of-life factors, some of which may be relevant to the assessment (e.g., in considering population susceptibility). An example of a set of quality-of-life criteria developed by the State of Vermont's Agency of Natural Resources is provided in Appendix F; however, it should be noted that quality-of-life issues can encompass much more than the criteria mentioned in this example. Some human health or ecological cumulative risk assessments may consider quality-of-life factors as having a role in susceptibility to the stressors being assessed.

3.3.2. The Promise of Biomarkers and Biomonitoring

There are a variety of measures that are inherently cumulative. These include biomarkers (they give the full effect or full exposure, regardless of source) and measures of the incidence and prevalence of disease in a community. The latter give an indication of the total effect of multiple sources of exposure. In light of our understanding of the multifactorial basis of disease, a public health approach that says "regardless of the cause, a community has x level of disease" can be informative. Such statistics can be compared across geographical areas that have different sources or groups that have different levels of vulnerability. The approach is based strongly in the field of epidemiology. Indeed, the most often-heard critique of epidemiology—that it is the prevalence or incidence of disease documented as a function of the combined effect of many exposures (over time and/or space)—is exactly what makes it so well suited for cumulative risk assessment. It is likely that epidemiological concepts will figure prominently in cumulative risk assessment, both in identifying the underlying vulnerability of a population and in generating hypotheses regarding the determination of relative contributions of multiple stressors (IPCS, 1983).

Sources of data include cross-sectional analyses that determine prevalence levels as well as basic surveillance techniques. With respect to the latter, The Pew Environmental Health Commission (http://pewenvirohealth.jhsph.edu/html/home/home.html) has recently completed a series of reports that document the extent of national- and state-level resources for chronic disease surveillance. Reports focus on the type of surveillance systems needed as well as the status of registries for birth defects and asthma. Health Track (http://health-track.org/ and http://healthyamericans.org/) is the outgrowth of that research; it is devoted to tracking and monitoring chronic disease to help communities to identify patterns of health problems.

Like epidemiologic data, some biomarkers reflect the cumulative history of individuals and populations. The use of biomarkers is based on the concept that the biological unit (organ, body, etc.) can be an effective and accurate element for integrating the aggregate exposures or doses or cumulative risks. Using biological measurements—biomarkers—to determine prior exposures (biomarkers of exposure) or the current health status of individuals (biomarkers of effect) holds some promise for cumulative risk assessments of the future (IPCS, 1993, 2001). Use of biomarkers for a group of chemicals or stressors that act upon individuals in the same way can give the assessor a picture of where an individual currently falls on the continuum from exposure to effects, making it much easier to predict risks if additional exposure occurs.

A few biomarkers (or even a single one) can possibly represent exposure to a suite of chemicals. Although this approach reduces the analytical burden and simplifies the process of estimating cumulative risk, it loses some of the advantages of single-chemical assessment (especially being able to quickly discern the importance of different pathways and routes of exposure contributing to the risk).

Biomarkers have a number of advantages; one disadvantage, however, is that they generally cannot link an effect to any particular exposure. For example, information on the cumulative risks in a local population of a group of chemicals that are toxic to the liver might be provided by selective liver function tests, but causal inferences would have to take account of many other factors that may affect liver function. Likewise, body burden data for chlorinated dioxins and related compounds may show that exposure has occurred, but assumptions would need to be made as to the pathways, route, and timing of exposures and scenarios developed for future exposures if risks are to be estimated. For a regulatory agency such as EPA, a decision to act to reduce risk often depends on separating contributions from exposure pathways so that effective policies can be determined.

One of the benefits of the biomarker approach—the development of data that show the actual current exposure and risk status of a population—is also its major impediment: it can require extensive (or for humans, possibly invasive) monitoring. Monitoring data can be not only costly, but also difficult to obtain. This approach uses primarily measurement methods; it can also be used to develop statements of probability of adverse effects of additional incremental exposures. This approach holds great promise for simplifying cumulative risk assessments, but few methods exist at this time for such applications. Although this framework report provides

only a cursory discussion of the biomarker approach, it is hoped that the planned guidelines for cumulative risk assessment will discuss this approach in greater detail.

3.3.3. A Single Metric for Multiple Types of Hazard

The most complex cumulative risk assessments will evaluate both multiple exposures (potentially, multiple sources, stressors, pathways, and durations) and multiple effects. Ideally this evaluation would provide projections regarding the potential for a particular complex exposure to cause particular effects to different physiological systems and also provide an integration of these projections into a qualitative characterization of overall potential impact to human health. Some applications have attempted to integrate the potential impacts across the different physiological systems. Approaches vary from treating the assessment as a number of multistressor, single-effect assessments, where the risks are combined only at the final step, to assessments that are more integrated throughout all the steps in the assessment process.

For example, cumulative ecological risk assessments conducted in the Columbia River Basin and the Chesapeake Bay (Barnthouse et al., 2000) focused on a number of observed adverse conditions, and then determined from among all the possible stressors, which particular combination was most influential in creating those conditions. Stressors such as over harvesting of natural resources; modification of natural hydrology; land use change; point-source and nonpoint-source pollution, including toxic chemicals; and the presence of exotic species were analyzed, with the goal of designing effective restoration strategies to eliminate or ameliorate the conditions.

If it is considered desirable for the assessment, an important activity may be to determine how (if at all possible) to combine risks from different effects—or the even-more-problematic disparate measures of risk—and present them in an integrated manner. Depending on the purpose and risk management objectives (see Section 2.1.1), some cumulative risk assessments may employ some sort of single, common metric to describe overall risk.

One—but certainly not the only—approach to simplifying this problem is to collapse this "n-dimensional matrix" of hazards and risks into a few or even a single measure (Murray, 1994). However, this requires converting the various measures of risk into a common metric or otherwise translating them into a common scale or index. Some methods for combining disparate measures of risk are briefly described below.

3.3.3.1. Creating a common metric

As discussed earlier in this chapter, there are several different theoretical approaches to cumulative risk assessment. Some of them require synthesizing a risk estimate (or risk indication) by "adding up" risks from different parts of the risk picture. Actual mathematical addition, of course, requires a "common denominator," or a common metric. Frequently used common metrics are risk, money, time, and effort. Finding a common metric for dissimilar risks (e.g., cancer vs. noncancer, human vs. ecological) is not strictly an analytic process, because some judgments should be made as to how to link two or more separate scales of risks. These judgments often involve subjective values, and because of this, it is a deliberative process.

EPA's Office of Pollution Prevention and Toxics has released a CD-ROM (USEPA, 1999i)[14] that shows an example of combining different effects into a common metric and the consequent judgment needed to achieve a common metric. In this model, emissions for both carcinogens and noncarcinogens are weighted by a toxicity factor so that they can be combined in a risk-based screening "score" for a particular geographic area. The scale for this weight for carcinogens is related to the unit risk factor, and the weight for the noncarcinogens is based on the RfD. According to the authors, it is possible to link these two different scales by making a deliberative judgment or assumption as to their relationship. They note that in their case, "when combining cancer and noncancer endpoints, it is assumed that exposure at the RfD is equivalent to a 2.5×10^{-4} cancer risk" (Bouwes and Hassur, 1998; USEPA, 1998h).

Obviously, as Bouwes and Hassur acknowledge, equating an HQ[15] value of 1.0 (i.e., exposure is at the RfD) with a cancer risk of 2.5×10^{-4} is a judgment that is outside the strictly analytic part of an assessment; the equating of the two points in the respective scales represents a value judgment and as such can be debated. Therefore, this particular part of the assessment is deliberative in nature. In making these types of judgments in a risk assessment, some care should be taken not to lose information in the aggregation, especially if all stakeholders do not agree on the relative tradeoffs necessary to arrive at the common scale of risk. If there is disagreement on constructing the scale, or even if more clarity is desired in the final report, the disaggregated risks can also be presented. Equity issues may also arise here, making it necessary to break out risks into relative burdens for different subpopulation.

In most cases, construction of a single scale for different types of endpoints will involve *comparative risk*, a field where different types of risks or endpoints are ranked, compared, weighted, or converted to a scale on the basis of the judgments and values of the persons doing the assessments (USEPA, 1990b, 1993b, 1998f, 1999j). Groups of stakeholders such as are

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[14] As of this writing, version 2.0 is in beta test. Details are available at <www.epa.gov/oppt/env_ind/beta_test.htm>.

[15] A hazard quotient, or HQ, in this context is the estimated exposure or dose level for a given individual chemical divided by the RfD (or RfC) for that chemical. Values of less than 1.0 for HQ indicate levels that are generally expected to be without effect during a lifetime.

gathered for cumulative risk assessment can provide ranking of various effects in terms of importance even if the effects cannot be put on a single scale or metric. This information may subsequently be used by decisionmakers for dealing with "worst risks first."

There have been some attempts to allow for transparent and quantitative incorporation of values into a common metric. One example flows from the suggestion that "time is the unit of measure for the burden of disease," whether the disease results in disability or premature mortality (Murray, 1994). On this premise, economic analyses of the costs and benefits of disease intervention strategies have used quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs) as the metrics for the adverse effects of disease. These metrics are intended to reflect the years of life spent in disease states (considering the variation in severity of effects) and the years of life lost due to premature mortality resulting from disease as a surrogate measure for risk from a variety of different types of effect.

Even if this conversion of effects into QALYs or DALYs is successful, for diseases that result in periods of morbidity and disability (but not death), weighting factors (based on judgments) are used to equate time spent in various disease states with years lost to mortality. In this way, dissimilar adverse effects can be combined to provide a single measure of disease burden. However, it should be noted that aggregation of effects in this manner obscures the meaning of the final measure. QALYs and DALYs do not represent an actual shortening of the life span but are indicators of the overall degradation of well-being that results from various disease states.

Experience with applying such measures as QALYs and DALYs to environmental risk problems is extremely limited. Some very early methods development work has been initiated that explores the use of QALYs for combining microbial and disinfection by-product risks (USEPA, 1998f). However, some concerns have been raised about the adequacy of such measures, especially when integrated with economic information for decision making (USEPA, 2000g). Further methods development work is needed to improve the usefulness of QALYs and DALYs for environmental risk assessments, especially with respect to the incorporation of uncertainty (USEPA, 1999j).

Categorical regression may provide another tool for combining disparate effects using a common metric. In this approach, adverse effects are assigned to severity categories (again, a judgment making the process deliberative) and the ordered categories are regressed against increasing dose (Teuschler et al., 1999). This use of categorical regression puts definite limits on the interpretation of the results. Because the toxicities are only represented by categories and judgment is used to place the observed response into a severity category, the results are rather coarse. But because the analysis is almost totally empirical—that is, no low-dose extrapolation is required—the results can still be quite useful.

EPA has also used decision indices (see Section 3.2.2.3) that are based on dissimilar measures, and although they do not produce risk estimates, they can still prove useful. The approach involves developing a composite score—or index—from measures of various risk dimensions. Various environmental risk indices have been developed and applied to ranking and

comparative analyses. Often, these indices use surrogate measures for risk rather than actual calculations of the probability of adverse effects. One such index is the HRS, which is used to place uncontrolled waste sites on the National Priorities List for Superfund. This index is based on the likelihood of off-site movement of waste, the toxicity of the waste, and the people and sensitive environments that may be affected. It also uses corrosivity, toxicity, fire hazard, and other factors, which are scored and combined into one numerical indicator of overall hazard potential. Such an approach for a composite index has been suggested for the communication of cumulative risk (Hertzberg, 2000).

Fischhoff et al. (1984) provides an example of this approach as applied to the evaluation of energy technologies. In this case, disparate risks are assigned a score from a fixed scale (e.g., from 0, representing no risk, to 100, representing the worst risk for that dimension). The scores are then weighted to reflect value judgments about the importance of the various risk dimensions, and the composite score is calculated by summing the individual weighted scores. Again, the aggregation of dissimilar adverse effects obscures the meaning of the final score, making this approach more appropriate for ranking and comparative analyses.

Recently, EPA has been working on several index-based approaches to dealing with cumulative risk issues. EPA Region 3 and the Office of Research and Development have been jointly working to develop a potential risk indexing system (USEPA, 1993c, 1995d, 1997c). This index also uses a vulnerability index, and it gauges the overall well-being of a locale and various subpopulations. Again, the volume and toxicity of released stressors serve as surrogate measures of risk in developing this index.

Combining the diverse effects and risk using either common metrics or indices has both pros and cons. A weakness of the index approach is that, by aggregating dissimilar information, information is "lost," and the meaning of the final score can be obscured. However, both approaches have one strength in common: the ability to incorporate social values into the risk assessment in an explicit and quantitative manner. For example, in the derivation of DALYs, weights can be used to reflect the different social roles people play as they age (Murray, 1994). In the composite scores developed by Fischhoff et al. (1984), public concern was incorporated as an adverse effect. The ability to incorporate issues suach as public concern into the composite scores is an important feature for methods that will be applied to cumulative risk assessments, especially for communities. Given that cumulative assessments have a community/population focus, the ability to incorporate social values into an overall assessment of well-being will be critical.

3.3.3.2. General issues regarding a single metric

As described above, each approach to portraying the results of a cumulative risk assessment has desirable and undesirable features. Although common metrics and indices can incorporate social values in an explicit and quantitative manner, the meaning of the final measure can be obscured by the aggregation of dissimilar effects. The abstract nature of the final measure could lead to difficulties when communicating the results of the assessment to the public. The use of graphical and mapping techniques do not necessarily overcome

communication problems. Although these techniques do not have some of the problems associated with the mathematical aggregation of dissimilar effects, it still may be difficult, for example, to accurately describe the information that a graphic is intended to convey.

Because we have relatively little experience in combining different types of risk, a key issue is *the need for methods development* in this area. The approaches described above indicate a beginning. Additional exploratory work is needed, however, to further develop existing methods and to find additional methods that are flexible, that can incorporate social values, that are easy to communicate, and that provide an integrated portrayal of the overall well-being of a community and its various subpopulations.

3.3.4. Qualitative Approaches

There will be cases where cumulative risk cannot be quantified in any meaningful or reliable way. Qualitative approaches can be valuable for cumulative risk assessment and, in the near term, they may be the only practical way to address many of the complexities involved. Qualitative approaches may be used as a way to overcome the complexity and data deficiencies that hinder quantitative approaches. In many assessments, risk may not be a quantifiable variable.

For these cases, there may be qualitative approaches that provide some insight. Broad indicators related to exposure in complex ways (e.g., production volumes, emissions inventories, environmental concentrations, etc.) and indicators of toxicity can be communicated using geographic information systems. Displaying complex, multidimensional matrices on a map can help in visualizing locations of areas with multiple stressors. Furthermore, geographically based measures of hazard are potentially useful cumulative measures; although they do not provide information on the risks, the locations of hazards can be used as an indicator of aggregate exposures and, thus, cumulative risks from all of the potential chemicals associated with that site. The environmental justice literature has used this approach.

Quantitative results might eventually be reduced to a more qualitative scale (high, medium, or low), or the qualitative results could provide "comments" tacked onto the quantitative results. The assessment might simply raise red flags associated with specific issues (e.g. density of emitters in a community, presence of minority populations, special exposure pathways, etc); a high number of such flags would indicate unacceptable cumulative risk, even if the risk is not quantified. This approach has been used in the European Union (CEU, 1996), and its experience in using qualitative methods for permitting suggests that "qualitative" is not "irrational." Other relevant tools include expert judgment techniques, focus groups, opinion surveys, citizen juries, and alternative dispute resolution.

4. THE RISK CHARACTERIZATION PHASE

The last phase of cumulative risk assessment, risk characterization, integrates and interprets the results of the analysis phase and addresses the problem(s) formulated in the planning and scoping phase (Figure 4-1). It should describe the qualitative and/or quantitative risk assessment results; list the important assumptions, limitations, and uncertainties associated with those results; and discuss the ultimate use of the analytic-deliberative outcomes. Given the complexity of cumulative risk issues and the need for clarity and transparency in risk characterization, such "full disclosure" presents a major communication challenge.

There is a substantial analytical component of the risk characterization phase, but there is also a considerable need for deliberation. At a minimum, stakeholders in this phase should (1) understand the outcome of the cumulative risk assessment, (2) ask questions about how best to frame the interpretation, and (3) confirm that the cumulative risk assessment met the goals set in the problem formulation, or if not, why not. As in the previous phase, the stakeholders' role is only limited by what is proposed and agreed upon in the particular case being assessed.

Risk estimation in a cumulative risk assessment will involve some combination of risks, whether the risks from different stressors cause similar effects or different types of effects. The stressors themselves may be similar or widely different. Combinations of many types of stressors that have different endpoints will quickly cause the risk estimation step to become very complex and difficult.

Because of its potential complexity, and because in some cases the cumulative risk assessment will be dealing methodologically with "uncharted territory," it is very important that the planning, conduct, analysis, and characterization of an assessment be transparent. As stated by the Office of Management and Budget (OMB, 2002), the "benefit of transparency is that the public will be able to assess how much an agency's analytic result hinges on the specific analytic choices made by the agency." The process, methodology, data, assumptions, and selection among alternate interpretations should be very carefully documented and very clearly stated. This is noted again in the next section.

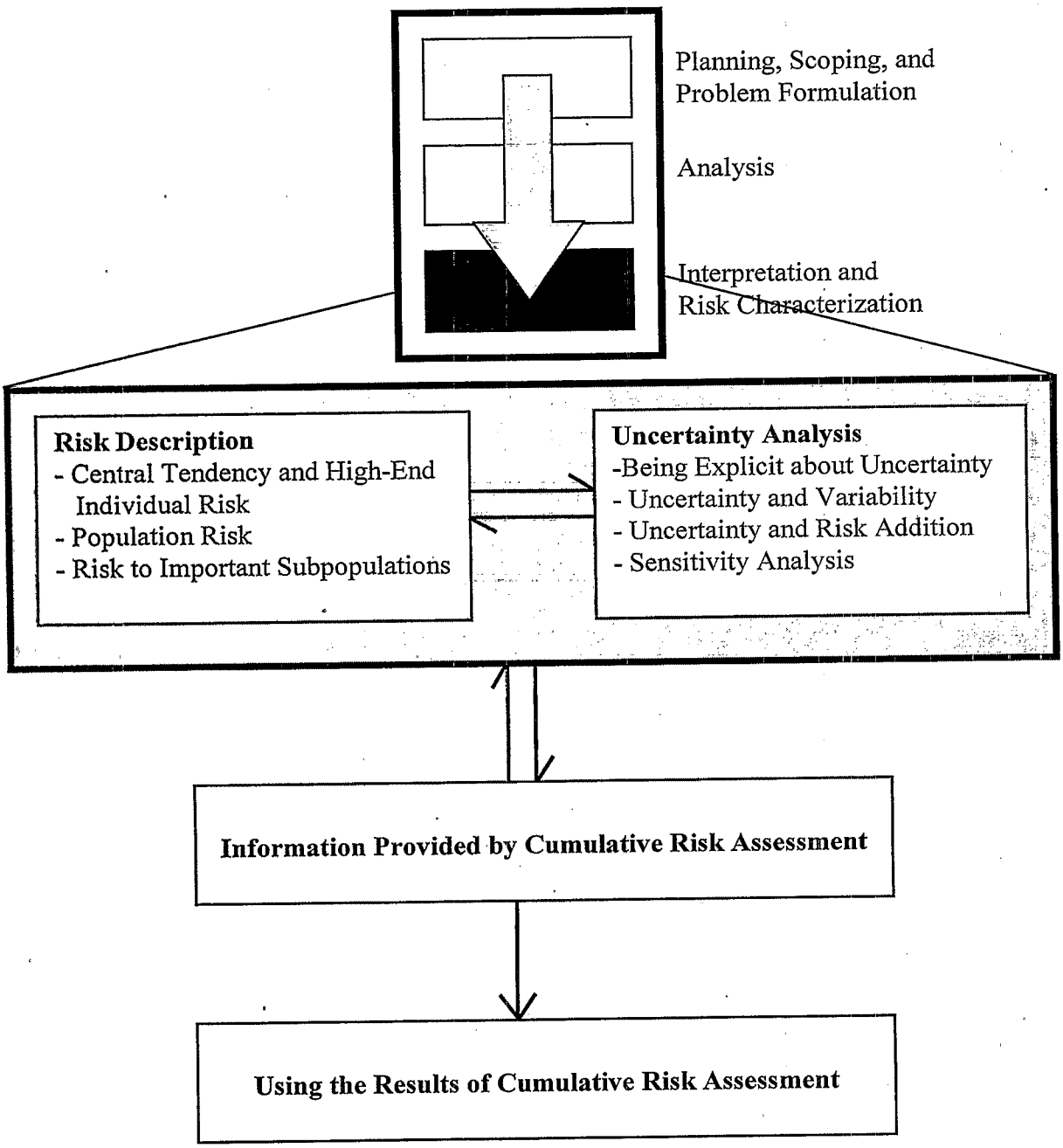

Figure 4-1. The Risk Characterization phase.

4.1. Risk Description

The ultimate product in the risk assessment process is the risk characterization, in which the information from all the steps is integrated and an overall conclusion about risk that is complete, informative, and useful for decisionmakers is synthesized. The nature of the risk characterization will depend on the information available, the regulatory application of the risk information, and the resources available (including time). It is important to identify and discuss all major issues associated with determining the nature and extent of the risk. Further, USEPA (1995a) specifies that a risk characterization "be prepared in a manner that is clear, transparent, reasonable, and consistent with other risk characterizations of similar scope prepared across programs in the Agency." In short, estimates of health risk are to be presented in the context of uncertainties and limitations in the data and methodology.

Risk Characterization Guiding Principles

Regarding information content and uncertainty aspects:

- The risk characterization integrates the information from the exposure and dose-response assessments using a combination of qualitative information, quantitative information, and information regarding uncertainties.
- The risk characterization includes a discussion of uncertainty and variability.
- Well-balanced risk characterizations present risk conclusions and information regarding the strengths and limitations of the assessment for other risk assessors, EPA decisionmakers, and the public.

Regarding risk descriptors:

- Information about the distribution of individual exposures is important to communicating the results of a risk assessment.
- Information about population exposure leads to another important way to describe risk.
- Information about the distribution of exposure and risk for different subgroups of the population are important components of a risk assessment.
- Situation-specific information adds perspective on possible future events or regulatory options.
- An evaluation of the uncertainty in the risk descriptors is an important component of the uncertainty discussion in the assessment.

Source: USEPA, 1995b

USEPA (1995b) lists several guiding principles for defining risk characterization in the context of risk assessment (see text box), both with respect to information content and uncertainty aspects and with respect to descriptions of risk. EPA has also published a handbook on risk characterization (USEPA, 2000c).

Risk assessments are intended to address or provide descriptions of risk to one or more of the following: (1) people exposed at average levels and people in the high-end portions of the risk distribution, (2) the exposed population as a whole, and (3) important subgroups or life stage strata of the population (e.g., children) or other highly susceptible groups or individuals, if known. Risk predictions for sensitive subpopulations are a subset of population risks. Sensitive subpopulations consist of a specific set of individuals who are particularly susceptible to adverse health effects because of physiological (e.g., age, gender, pre-existing

Some Thoughts on Risk Characterization

Understanding Risk (NRC, 1996) focuses on risk characterization and reaches the following conclusions:

1. Risk characterization should be a *decision-driven activity*, directed towards informing choices and solving problems. The view of risk characterization as a translation or summary is seriously deficient.... Risk characterization should not be an activity added at the end of risk analysis; rather, its needs should largely determine the scope and nature of risk analysis.

2. Coping with a risk situation requires a *broad understanding* of the relevant losses, harms, or consequences to the interested and affected parties. A risk characterization must address what the interested and affected parties believe to be at risk in the particular situation, and it must incorporate their perspectives and specialized knowledge.

3. Risk characterization is the outcome of an analytic-deliberative process.... Analysis and deliberation can be thought of as two complementary approaches to gaining knowledge about the world, forming understandings on the basis of knowledge, and reaching agreement among people.

4. The analytic-deliberative process leading to a risk characterization should include early and explicit attention to *problem formulation.*

5. The analytic-deliberative process should be *mutual and recursive.*... A recurring criticism of risk characterization is that the underlying analysis failed to pay adequate attention to questions of central concern to some of the interested and affected parties. This is not so much a failure of analysis as a failure to integrate it with broadly based deliberation: the analysis was not framed by adequate understanding about what should be analyzed.... Structuring an effective analytic-deliberative process for informing a risk decision is not a matter for a recipe. Every step involves judgment, and the right choices are situation dependent. Still, it is possible to identify objectives that also serve as criteria for judging success:

Getting the science right. The underlying analysis meets high scientific standards in terms of measurement, analytic methods, databases used, plausibility of assumptions, and respectfulness of both the magnitude and character of uncertainty....

Getting the right science. The analysis has addressed the significant risk-related concerns of public officials and the spectrum of interested and affected parties, such as risks to health, economic well-being, and ecological and social values, with analytic priorities having been set so as to emphasize the issues most relevant to the decision.

Getting the right participation. The analytic-deliberative process has had sufficiently broad participation to ensure that the important, decision-relevant information enters the process, that all important perspectives are considered, and that the parties' legitimate concerns about inclusiveness and openness are met.

Getting the participation right. The analytic-deliberative process satisfies the decision makers and interested and affected parties that it is responsive to their needs: that their information, viewpoints, and concerns have been adequately represented and taken into account; that they have been adequately consulted; and that their participation has been able to affect the way risk problems are defined and understood.

Developing an accurate, balanced, and informative synthesis. The risk characterization presents the state of knowledge, uncertainty, and disagreement about the risk situation to reflect the range of relevant knowledge and perspectives and satisfies the parties to a decision that they have been adequately informed within the limits of available knowledge.

6. Those responsible for a risk characterization should begin by developing a *diagnosis of the decision situation* so that they can better match the analytic-deliberative process leading to the characterization to the needs of the decision, particularly in terms of level and intensity of effort and presentation of parties.... Diagnosis of risk decision situations should follow eight steps: (1) diagnose the kinds of risk and the state of knowledge, (2) describe the legal mandate, (3) describe the purpose of the risk decision, (4) describe the affected parties and anticipate public reactions, (5) estimate resource needs and timetable, (6) plan for organizational needs, (7) develop a preliminary process design, and (8) summarize and discuss the diagnosis with the responsible organization.

conditions), socioeconomic (e.g., nutrition), or demographic variables or because of significantly greater levels of exposure (USEPA, 1992a). Subpopulations can be defined using age, race, gender, and other factors. If enough information is available, a quantitative risk estimate for a subpopulation can be developed; if not, then any qualitative information about subpopulations gathered during hazard identification should be summarized as part of the risk characterization (USEPA, 2000c). The box on the previous page summarizes some of the points made in *Understanding Risk* (NRC, 1996), which devotes a great deal of discussion to risk characterization. Risk characterization is most efficiently conducted with early and continued attention to the risk characterization step in the risk assessment process (NRC, 1996; USEPA, 2000c).

4.2. Uncertainty Analysis

Morgan and Henrion (1990) note that, historically, the most common approach to uncertainty in policy analysis (including in risk assessment) has been to ignore it. In a section titled "Why Consider Uncertainty?" they advance three primary reasons, all of which are especially relevant to an analytic-deliberative process such as cumulative risk assessment. They suggest that it is important to worry about uncertainty

- "when one is performing an analysis in which people's attitude toward risk is likely to be important, for example, when people display significant risk aversion;
- "when one is performing an analysis in which uncertain information from different sources must be combined. The precision of each source should help determine its weighting in the combination; and
- "when a decision must be made about whether to expend resources to acquire additional information. In general, the greater the uncertainty, the greater the expected value of additional information."

Morgan and Henrion provide ten requirements for good policy analysis, and although all are commendable and several have been discussed elsewhere in this framework report, we should look more closely at numbers 6–8 in the box at right for some insight into uncertainty analysis.

Morgan and Henrion's Ten Requirements for Good Policy Analysis

1. Do your homework with literature, experts, and users.
2. Let the problem drive the analysis.
3. Make the analysis as simple as possible, but no simpler.
4. Identify all significant assumptions.
5. Be explicit about decision criteria and policy strategies.
6. Be explicit about uncertainties.
7. Perform systematic sensitivity and uncertainty analysis.
8. Iteratively refine the problem statement and the analysis.
9. Document clearly and completely.
10. Expose the work to peer review.

Source: Morgan and Henrion, 1990

There are many resources available that talk in detail about how to perform uncertainty analysis (e.g., USEPA, 1997b; Morgan and Henrion, 1990). Although detailed instruction is beyond the scope of this framework report, we believe that a discussion of some general principles is in order.

4.2.1. Assumptions in the Assessment

Cumulative risk assessment will typically be used in a decision-making process to help inform the decisionmaker(s). For this reason, it is important that the decisionmakers be made explicitly aware of any assumptions that may significantly affect the conclusions of the analysis (requirement number 4 in the box on previous page). Morgan and Henrion (1990) suggest that these assumptions include:

- the main policy concerns, issues, or decisions that prompted the assessment,
- the evaluation criteria to be used to define issues of concern or options,
- the scope and boundaries of the assessment and ways in which alternate selections might influence the conclusions reached,
- soft or intangible issues that are ignored or inadequately dealt with in the quantitative analysis (e.g., intrinsic value of wilderness, equity of distribution of risks and benefits),
- approximations introduced by the level of aggregation or by level of detail in models,
- value judgments and tradeoffs, and
- the objective function used, including methods of combining ratings on multiple criteria (or combining risk scales).

Identifying significant assumptions can often highlight "soft" uncertainties that are not easily quantified and are therefore often left out of a quantitative uncertainty analysis. Nevertheless, these "soft" uncertainties can often contribute more to the overall uncertainty of the assessment than the factors more easily quantified.

Morgan and Henrion's sixth requirement for good policy analysis (see box on previous page) includes three types of uncertainty that analysts should explicitly address:

- Uncertainty about technical, scientific, economic, and political quantities (e.g., quantities such as rate constants often lend themselves to quantitative uncertainty estimates relatively easily);
- Uncertainty about the appropriate functional form of technical, scientific, economic, and political models (e.g., are the models used, such as dose-response models, biologically sound?); and
- Disagreements among experts about the values of quantities or the functional form of models (e.g., different health scientists using different forms of dose-response models).

In requirement number 7, Morgan and Henrion suggest that an assessor should find out which assumptions and uncertainties may significantly alter the conclusions, and that this process can be conducted using sensitivity and uncertainty analysis. Techniques include:

- Deterministic, one-at-a-time analysis of each factor, holding all others constant at nominal values;

- Deterministic joint analysis, changing the values of more than one factor at a time;
- Parametric analysis, moving one or a few inputs across reasonably selected ranges to observe the shape of the response; and
- Probabilistic analysis, using correlation, rank correlation, regression, or other means to examine how much of the uncertainty in the conclusions is attributable to which inputs.

Finally, Morgan and Henrion answer the question of why we should consider uncertainty analysis with the following point. "Policy analysts have a professional and ethical responsibility to present not just 'answers' but also a clear and explicit statement of the implications and limitations of their work. Attempts to fully characterize and deal with important associated uncertainties help them to execute this responsibility better."

4.2.2. Uncertainty and Variability

NRC (1994) notes a clear difference between uncertainty and variability and recommends that the distinction between these two be maintained:

> A distinction between uncertainty (i.e., degree of potential error) and inter-individual variability (i.e., population heterogeneity) is generally required if the resulting quantitative risk characterization is to be optimally useful for regulatory purposes, particularly insofar as risk characterizations are treated quantitatively. The distinction between uncertainty and individual variability ought to be maintained rigorously at the level of separate risk-assessment components (e.g., ambient concentration, uptake, and potency) as well as at the level of an integrated risk characterization.

The Cumulative Exposure Project

EPA's Cumulative Exposure Project (CEP), completed in 1998, modeled 1990 outdoor concentrations of hazardous air pollutants (HAPs) across the United States, which were combined with unit risk estimates to estimate the potential increase in excess cancer risk from multiple HAPs. The cancer risks of different HAPs were assumed to be additive and were summed across pollutants in each census tract to estimate a total cancer risk in each census tract.

Consideration of some specific uncertainties, including underestimation of ambient concentrations, combining upper 95% confidence bound potency estimates, and changes to potency estimates, found that cancer risk may be underestimated by 15% or overestimated by 40-50%. Other unanalyzed uncertainties could make these under- or overestimates larger.

Source: Woodruff et al., 2000

Variability and uncertainty have been treated separately and distinctly in single-chemical assessments such as the assessment of TCE in ground water at Beale Air Force Base in California (Bogen, 2001). The treatment of variability and uncertainty will also be an important issue in cumulative risk assessments, although at the time of this writing there are no good examples of an elegant treatment of this issue for cumulative risk.

4.2.3. Uncertainty and Risk Addition

Calculating individual stressor risks and then combining them largely presents the same challenges as combination toxicology but also adds some statistical stumbling blocks. Toxicity addition, independence, synergism, or antagonism still need to be evaluated, but because risk estimates for various stressors are often presented as values on the same numeric scale (e.g., as cancer probabilities), cancer risks are often simply added together.

Because cancer slope factors are not "most probable estimates," but rather 95% upper confidence levels, adding traditional risk levels can cause the resulting sum to overestimate a 95% upper confidence level risk for a mixture. There have been several recent papers discussing this problem and how it may affect the resulting estimates. Kodell and Chen (1994) looked at several binary mixtures and calculated that the summation of individual upper 95% confidence intervals for chlorobenzene and hexachlorobenzene would overestimate the upper-bound risk of a binary mixture of these compounds by 2 to 6%, whereas for chlorobenzene and TCE the overestimate would be in the range of 12 to 15%. Seed et al. (1995) noted that, "in most cases, the magnitude of the difference in cancer risk estimates calculated by [Kodell and Chen's] various methods will be greatest for mixtures of equipotent compounds. However, even for mixtures of equipotent compounds, the differences in joint risk estimated by summing the upper 95% confidence levels...are not great."

After analyzing four cases, Cogliano (1997) concluded that "as the number of risk estimates increases, their sum becomes increasingly improbable, but not misleading." For example, in adding 20 different cancer risk estimates based on a 95% upper bound, the resulting sum of the upper bounds was no more than 2.2 times the true upper bound. Cogliano went on to suggest that, for certain cases not involving synergistic or antagonistic interactions, "depending on the number of carcinogens and the shape of the underlying risk distributions, division by a factor of 2 can be sufficient to convert a sum of upper bounds into a plausible upper bound for the overall risk."

The assumption of toxicologic independence (see Section 3.2.2) may not be a bad one if other evidence supports it, but it should be addressed in the assessment if used (i.e., if risks are added). Although some scientists believe that toxicologic interactions are of minor consequence at concentrations observed in the environment (see discussion in USEPA, 2000e), the scientific evidence for such an assumption has not been firmly established.

Notwithstanding the statistical limitations of adding traditional risk estimates and the implicit assumption that the toxicities will be additive[16] (i.e., no interactions such as synergism or antagonism occur), the numerical ease for combining risks in this way may make it the most

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[16] At risk levels often seen with pollutant concentrations observed in the environment, the combined risks calculated assuming "response additivity" (that is, each component acts as if the other were not present) are approximately the same as with dose additivity (USEPA, 2000e).

popular method for approximating cumulative risks in the short term, at least at a screening level of assessment.

4.2.4. Other Cumulative Risk Assessment Uncertainties

This framework does not, and cannot, provide an exhaustive list of uncertainties unique to cumulative risk assessment. Without question, however, there will be uncertainties inherent in a cumulative risk analysis that have not been as important in traditional assessments. As an example, because cumulative risk assessments can be geographically based and GIS technology seems to be a potentially useful tool for displaying results, there will be issues concerning how to present uncertainty information, for example, by overlaying impacts or risks for several chemicals, on a GIS map.

Specific uncertainties can arise when adding doses for chemicals that operate by the same mode of action, such as the organophosphorous (OP) pesticides. In this case, USEPA (2002c) notes that uncertainties arise in estimating the RPFs of the OP pesticides. These RPF uncertainties can be partitioned into three groups: those that are basic (e.g., uncertainty in the dose-response relationship for the reference chemical), those that deal with chemicals in relation to one another (relative potencies of other chemicals relative to the reference chemical), and those concerning joint mode of action (e.g., members of the common mechanism group may have other modes of action that are not fully captured via the common-mechanism potency calculation). As risk assessors develop more experience with cumulative risk assessments, many more of these uncertainties may arise, but it is not possible to foresee all of them.

4.3. Information Provided by Cumulative Risk Assessment

It is important to clarify how cumulative risk assessment and this framework report relate to community assessments and community decision making. Certainly, the Agency's risk characterization handbook (USEPA, 2000c) emphasizes that whatever information is imparted should be transparent, clear, consistent, and reasonable. For example, if it is known that the results of a particular cumulative risk assessment will be severely limited because of a lack of data or available methods, it may be advisable to start with a screening analysis to set priorities for a subsequent study that is more detailed and focused. In simple terms, what can a cumulative risk assessment tell us, and what can't it tell us?

4.3.1. Making Sense of Multiple-Stressor Effects

The information provided by cumulative risk assessment is only a portion of that needed by communities and governments to make informed decisions about risks. There are almost always a multitude of factors that affect health in a community (e.g., crime, drugs, health care access, vehicle safety, climate, infectious disease, diet) that may not have been considered within the scope of a given cumulative risk assessment. Community decision making will typically take into account risks to the environment as well as consideration of historical and cultural values and questions of fairness and distribution of risks. The methodology is not currently available to understand how these factors (or stressors) may affect cumulative health risk.

Additionally, benefits such as jobs and useful products or services that may be associated with chemical or other stressor exposures may be important contexts for decisions on the risks considered in cumulative risk assessments.

This framework report is not an attempt to lay out protocols to address all the risks or considerations that are needed to adequately inform community decisions. Rather, its focus is on describing various aspects of cumulative risk, *whether or not the methods or data currently exist to adequately analyze or evaluate those aspects of the assessment*. It devotes considerable time to a discussion on improving the methods for a single part on the broader picture: characterizing health risks associated with exposures to multiple chemicals via multiple routes. Because of the limitations of the current state of the science, cumulative risk assessments in the near future will not be able to adequately answer all the questions posed by stakeholders or interested parties. This does not mean, however, that they would not be useful in providing insights to *some* of the questions asked; in fact, cumulative risk assessment may be the best tool available to address certain questions dealing with multiple-stressor impacts.

4.3.2. Cumulative Risk Assessments in a Public Health Context

The public often asks—in a variety of ways—for clarification of the relationship between environmental pollution (and risk assessments concerning it) and public health. Although cumulative risk assessment holds the promise of better public health-related information for communities, it is not a panacea. To draw relationships between environmental pollutant exposures and disease incidence, a body of epidemiological study is necessary. Trying to "work backwards" from health statistics to risk factors requires full knowledge of the risk factors associated with the relevant disease(s). This is challenging under the best of circumstances, with good data; many times it is not possible with the data at hand.

Health statistics, including death rates and incidence of various diseases, illustrate the impact of a variety of risk factors (e.g., smoking as well as environmental pollutants) and risk reduction factors (e.g., exercise and good nutrition as well as pollution control measures). Indeed, population health statistics are reflective of *all* risk and risk reduction factors in a population's history to date. Even the best cumulative risk assessment, given today's state of the science, could not include an evaluation of the magnitude and interactions of *all* stressors and their effects. At best, the risk estimates of a cumulative risk assessment will reflect *some* of the risks that may be reflected in community health statistics. With rare exceptions[17], cumulative risk assessment estimates would not be expected to match exactly with community health statistics, even for specific health endpoints such as specific cancers.

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[17] It is conceivable that high risks to rare specific effects could be comparable for a risk assessment and community health statistics, given current state of the art. To be sure this is not coincidental, a substantial effort to match risk assessment scenarios with actual histories or exposures would have to be made.

4.3.3. How the Scope and Purpose of the Assessment Affect Results

Historically, the Agency's risk assessments have focused on assessing the risks from environmental pollutants to public health or the environment, usually for the purposes of prioritizing risk management activities or triggering regulatory action. Given the need for public health-protective decisions, traditional risk assessment tools usually focus on predicting high ends of the risk distribution. Also, the traditional tools are not designed to predict risk of diseases other than cancer. Additionally, the many environmental pollutants make up only some of the categories of risks to public health. Although quite adequate for their original purpose, when the results of these types of assessments are viewed from another perspective, such as that of a community concerned about the cumulative health impacts of five industrial and commercial facilities within a two-block area, they may not be useful.

The Agency is doing more place-based human health and ecological assessments (i.e., compared to source- or media-specific assessments) than in the past, but it will be some time before they become commonplace. Consistent with good practices for planning and scoping, they often may be driven by specific risk-management needs. The desired objectives and purpose of parties who were outside the process may differ from those for which the assessment was designed. For this reason, users of cumulative risk assessments are advised to carefully study the scope and purpose of the assessment at hand as well as the analysis plan and resulting characterization to determine whether it is suitable (or partly suitable) to answer questions outside its stated objectives and purpose.

4.3.4. Documenting Stakeholder Input

Somewhere in the discussion of how the assessment meets or does not meet the objectives laid out in the planning and scoping phase, it is useful to document how stakeholder input has influenced the process, noting also those suggestions that were not included and why. This documentation supports stakeholder participation and provides assurance that individuals have been heard.

4.4. Using the Results of the Assessment

Once the results of an assessment are in hand, the assessment participants will usually focus primarily on the communication and use of those results. The intended use of the assessment was considered at the beginning, in the problem formulation phase, both to plan the assessment work and to set the stage for possible actions that might be taken at this point. A detailed discussion of the communication and use of the results of a cumulative risk assessment is beyond the scope of this document, but it should be noted that in deciding on a course of action, considerations other than the results of the assessment will also need to be taken into account.

If the goals of a cumulative risk analysis are to estimate the risk from multichemical and multipathway exposure to people living within a geographical area of concern, then an

important objective in presenting the results is to identify the major risk contributors in order to understand the sources, pathways, and stressors that contribute most to that overall risk. The results of a cumulative risk assessment provide an additional tool for the risk manager, one that permits a more complete accounting and more explicit analysis to target follow-up risk mitigation strategies toward those stressors that most contribute to the population's risk.

If action to mitigate or prevent risk is the goal of the stakeholders, then the options for action discussed in the planning of the assessment can be re-evaluated in light of the results of the assessment. Some questions that might arise from this re-evaluation include: "Is regulatory authority available to address concerns or are voluntary actions better suited to address the risks?" or "Can the concerns be addressed by the stakeholders involved in the assessment or are the options for mitigation and prevention beyond the scope of their control?" In the latter case, for example, siting issues are usually decided locally and may be within the authority of the participants of a local assessment. In contrast, risk from mobile sources or acid rain are likely to require action that is beyond the scope of a single local community. In that case, taking action will require working with other communities and is likely to take more time. Discussion of the options available for addressing the results of a risk assessment will help to keep expectations in line with possibilities.

With regard to taking—or not taking—action after a cumulative risk assessment has been interpreted, the team may benefit from lessons learned by others, just as in the planning, scoping, and problem formulation phase. In early 2002 the European Environment Agency (EEA, 2001) released an extensive study of 12 classic case studies in human and environmental health protection and the lessons learned from them (see text box on the next page). The report is available on the Internet and should be food for thought for any group contemplating protective actions, particularly for community assessments.

Finally, it is important to keep in mind that the results of the risk assessment are only one of the factors to be considered in making a decision on action to address the risk. Risk information can make an important and valued contribution to the decision-making process, but it cannot by itself determine the decision. Factors such as the availability of resources for change; perceived fairness; politics; business and employment; quality-of-life issues; the religious, cultural, aesthetics, or social values of a community; or concern for future generations may also influence decisions.

In the siting example mentioned above, the assessment may determine that the new facility does not significantly increase risk to the community but a decision not to site the facility might still be made on the basis of a quality-of-life issue that is unrelated to risk. Or, a community may decide that the economic and employment benefits outweigh the risks associated with the siting. Other risk factors not considered in the assessment may also enter into the decision-making process, including both the environmental risks not covered in the cumulative risk assessment and the nonenvironmental risks that may affect a community. With limited resources, a community may use all available risk information to most effectively target its resources.

The European Environment Agency's 12 Lessons Learned Late

- Acknowledge and respond to ignorance, as well as uncertainty and risk, in technology appraisal and public policy-making.
- Provide adequate long-term environmental and health monitoring and research into early warnings.
- Identify and work to reduce blind spots and gaps in scientific knowledge.
- Identify and reduce interdisciplinary obstacles to learning.
- Ensure that real world conditions are adequately accounted for in regulatory appraisal.
- Systematically scrutinize the claimed justifications and benefits alongside the potential risks.
- Evaluate a range of alternative options for meeting needs alongside the option under appraisal, and promote more robust, diverse and adaptable technologies so as to minimize the costs of surprises and maximize the benefits of innovation.
- Ensure use of "lay" and local knowledge as well as relevant specialist expertise in the appraisal.
- Take full account of the assumptions and values of different social groups.
- Maintain regulatory independence from interested parties while retaining an inclusive approach to information and opinion gathering.
- Identify and reduce institutional obstacles to learning and action.
- Avoid "paralysis by analysis" by acting to reduce potential harm when there are reasonable grounds for concern.

Source: EEA, 2001

5. GLOSSARY

Adverse effect - A biochemical change, functional impairment, or pathological lesion that either singly or in combination adversely affects the performance of the whole organism or reduces an organism's ability to respond to an additional environmental challenge.

Agent - a chemical, physical, or biological entity that may cause deleterious effects in an organism after the organism is exposed to it.

Aggregate exposure - The combined exposure of an individual (or defined population) to a specific agent or stressor via relevant routes, pathways, and sources.

Aggregate risk - The risk resulting from aggregate exposure to a single agent or stressor.

Benchmark dose (BMD) - The dose producing a predetermined, altered response for an effect. A BMD_{10}, for example, would be calculated on the basis of a benchmark response of 10%.

Benchmark response (BMR) - A predetermined level of altered response or risk at which the benchmark dose is calculated. Typically, the BMRs used are 1%, 5%, or 10%.

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

Cumulative risk - The combined risks from aggregate exposures to multiple agents or stressors.

Cumulative risk assessment - An analysis, characterization, and possible quantification of the combined risks to health or the environment from multiple agents or stressors.

Dose additivity - In a mixture, when each chemical behaves as a concentration or dilution of every other chemical. The response of the combination of chemicals is the response expected from the equivalent dose of an index chemical (the chemical selected as a basis for standardization of toxicity of components in a mixture). The equivalent dose is the sum of component doses scaled by their toxic potency relative to the index chemical. For example, for chlorinated dibenzodioxins (CDDs), 2,3,7,8-TCDD is selected as the index chemical; other CDD concentrations are adjusted for their potency relative to 2,3,7,8-TCDD and then treated as if they were 2,3,7,8-TCDD "equivalents."

Dose-response relationship - A relationship between (1) the dose, either "administered dose" or absorbed dose and (2) the extent of toxic injury produced by that chemical or agent. Response can be expressed either as the severity of injury or the proportion of exposed subjects affected.

Endpoint - An observable or measurable biological or chemical event that is used as an index of the effect of a stressor on a cell, tissue, organ, organism, etc.

Exposure pathway - The physical course that a chemical or pollutant takes from the source to the organism exposed.

Exposure route - The way a chemical or pollutant enters an organism after contact, for example, by ingestion, inhalation, or dermal absorption.

Lowest-observed-adverse-effect level (LOAEL) - The lowest dose or exposure level at which there is a statistically or biologically significant increase in the frequency or severity of an adverse effect in the exposed population as compared with an appropriate, unexposed control group.

Model - A mathematical representation of a natural system that is intended to mimic the behavior of the real system, allowing description of empirical data and predictions about untested states of the system. Use of models is usually facilitated by computer programming of the mathematics and construction of a convenient input and output format.

No-observed-adverse-effect level (NOAEL) - An exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered to be adverse or precursors to adverse effects. In an experiment with several NOAELs, the common usage of the term NOAEL is the highest exposure without adverse effects.

Reference concentration (RfC) - An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime.

Reference dose (RfD) - An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime.

Response additivity - In a mixture, when the toxic response (rate, incidence, risk, or probability of effects) from the combination is equal to the conditional sum of component responses as defined by the formula for the sum of independent event probabilities. For two chemical mixtures, for example, the body's response to the first chemical is the same whether or not the second chemical is present.

Risk - *Absolute risk:* The probability of injury, disease, or death under specific circumstances. In quantitative terms, risk is expressed in values ranging from zero (representing the certainty that there is no chance of harm) to one (representing the certainty that harm will occur). *Incremental risk:* The probability of injury, disease, or death under specific circumstances, relative to the background probability. In quantitative terms, risk is expressed in values ranging

from zero (representing the certainty that the probability of harm is no greater than the background probability) to one (representing the certainty that harm will occur).

Stakeholder - An interested or affected party in an ongoing or contemplated project (usually involving a group or team planning the project, analyzing one or more problems, and making decisions for possible actions on the basis of the interpretation of that analysis).

Stressor - Any physical, chemical, or biological entity that can induce an adverse response. A stressor may also be the lack of an essential entity, such as a habitat.

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APPENDIX A: RESEARCH AND DEVELOPMENT NEEDS

Framework for Cumulative Risk Assessment is intended to provide a basic structure for the issues and define key terms and concepts. In some cases, the concepts introduced in the framework report require the application of knowledge and methods that are not currently available. The following is a discussion of the needed areas of research and methods development highlighted within the report that may be most important to an evaluation of cumulative risks. This is not intended to be a comprehensive listing of cumulative risk assessment research needs.

EPA and other scientists are currently investigating the use of similar approaches for cancer and noncancer assessments. Although we do not discuss this research need here, it would be useful to cumulative risk assessment to have similar approaches, and it is a topic of current discussion within scientific circles (e.g., Albert, 1999).

Understanding the Timing of Exposure and its Relationship to Effects

A key concept in the definition of cumulative risk is that it represents an accumulation of risk **over time**. However, unlike the traditional approach to risk assessment, where exposure events are summed and averaged over a period of time, cumulative risk assessment involves developing an understanding of how the sequence and timing of exposures influence the ultimate risk for effects. For example, for multiple stressors, it is important to understand how prior exposures to one or several stressors influence the risks from subsequent exposures to the same or different stressors. In addition, it is important to understand the implications of these exposures occurring during critical periods of an individual's life (e.g., important periods of development or periods of disease). Several exposure models are under development that recognize the need to understand the timing of various exposure events (e.g., Calendex, APEX, Lifeline, SHEDS, and CARES/RExY).

In addition to gaining a better understanding of the sequence and timing of exposures and their relationship to effects, it is important to understand how acute, nonlethal exposures from accidents contribute to chronic or long-term effects.

Understanding the Composition and Toxicity of Mixtures

Chemical mixtures can change or degrade over time and space, making the assessment of exposure a particular challenge. For cumulative risk assessment, the composition of the mixture at the point of contact with the receptor should be well characterized. Measurement techniques (at the receptor) and predictive models are both applicable in this characterization.

EPA's guidance for the health risk assessment of chemical mixtures (USEPA, 2000e) presents approaches for combining the toxicities of multiple chemical stressors. These approaches necessarily involve a number of simplifying assumptions when the mixtures are complex. Although the current methods provide a valuable resource for assessing cumulative

risks, future cumulative risk assessment will need a more complete understanding of the interactions among chemicals in complex mixtures. Some current research efforts are seeking to identify toxicologic principles of joint action that are applicable to mixtures involving many chemicals.

Applying the Risk Factor Approach to Environmental Health Risks

The risk factor approach has been used in the medical profession to predict the chances of individuals developing various diseases. It has proved to be a useful approach not only in assessing certain cumulative risks, but also in communicating with patients. In this approach, characteristics of a population (e.g., age, ethnicity, personal habits, genetic polymorphisms, prior diseases, etc.) are correlated with the incidence of disease. For some diseases (e.g., breast cancer, coronary artery disease, stroke) these correlations are well established. However, there are substantial data gaps in terms of the role played by exposures to environmental stressors in the development of human disease, and correlations of environmental exposures with disease outcomes are generally not available.

Using Biomarkers and Biomonitoring

The use of biomarkers of exposure or effect holds a great deal of promise for cumulative risk assessment. This approach can provide a method for assessing stressors in groups. Currently, however, this approach is not practicable when considering a large number of diverse stressors, because appropriate biomarkers for many types of stressors have not yet been developed.

Considering Hazards Presented by Nonchemical Stressors

Cumulative risk assessment could encompass the interactions of chemical stressors with biological, radiological, and other physical stressors; socioeconomic stressors; and lifestyle conditions. In trying to assess all these different types of stressors, it is helpful to determine what types of effects the stressors produce and then to try to group stressors by like effects. Ideally, one would like to know the mechanism or mode of action by which various stressors cause effects to allow a more refined grouping. Currently, however, there are few methods for understanding how these disparate stressors interact to result in risk.

Considering Psychological Stress as Part of Cumulative Risk

Psychological stress causes both psychological and physiological changes that can be measured. However, assessing levels of stress and their potential contribution to risk is difficult for a variety of reasons. The Agency for Toxic Substances and Disease Registry began the process of identifying research needs in this area through an expert panel workshop held in 1995.

Considering All Aspects of Vulnerability

The issue of the vulnerability of a population can be thought of as having four components: susceptibility of individuals, differential exposures, differential preparedness to withstand the insult, and differential ability to recover from effects. Traditional risk assessment may consider one or more of these categories, but rarely are all considered. The overall consideration of all four categories may be more important in cumulative risk assessment than in traditional one-chemical assessments. A cumulative risk assessment, for example, may need to consider potential combinations of high exposure and high vulnerability across stressors. Methods development work is needed in this area.

Methods for Combining Different Types of Risk

Another key concept in the definition of cumulative risk assessment is that such an assessment represents the combined risk from multiple stressors. This implies that, in some cases, it may be necessary to combine disparate measures of risk (i.e., different types of effects) to simplify the expression of cumulative risks. There have been some attempts to collapse complex arrays of risk into a few or even a single measure. These approaches have involved the use of common metrics (e.g., quality-adjusted life years, disability-adjusted life years, loss of life expectancy, etc.) and indices (e.g., hazard ranking system, etc.) and the categorization of effects (e.g., as for categorical regression). Alternatively, geographic information systems and mapping techniques can be used to graphically portray integrated information on risks without mathematically combining disparate measures. Much methods development work remains to be completed in each of these areas.

Development of Default Values for Cumulative Risk Assessments

Conventional risk assessments use a series of default values for screening or other applications, and it may be necessary to investigate whether certain defaults need to be established specifically for cumulative risk assessments.

Development of Case Studies and Issue Papers on Specific Cumulative Risk Topics

The more detailed technical issues and methodologies should be developed as a series of issues papers that would augment the framework report. The level of detail would, of course, vary, depending on the topic. The issues papers (or white papers) should also include details on additional approaches to cumulative risk assessment that are currently being explored (including screening-level analyses, place-based assessments, comparative risk assessments, National Environmental Policy Act cumulative effects analyses, and hazard assessments). In addition, the issues papers could include summaries of case studies of cumulative risk projects that would extend the framework from theoretical to practical approaches and applications.

APPENDIX B: SELECT RESOURCES FOR EXPOSURE AND RISK ASSESSMENT

B.1. Resources Relevant to Chemical Exposures

EPA Guidelines:

Most of EPA's general guidelines are listed in the text box in Section 1.1.

Air-related sources and activities:

EPA's Clearinghouse for Inventories and Emission Factors (CHIEF) website (www.epa.gov/ttn/chief/) is an excellent starting place. It has many of the relevant documents on methods and data for constructing emissions inventories available for download, including *Handbook for Criteria Pollutant Inventory Development: A Beginner's Guide for Point and Area Sources* (USEPA, 1999k), *Handbook for Air Toxics Emission Inventory Development, Volume I: Stationary Sources* (USEPA, 1998i), and the two volumes and supplement of *Compilation of Air Pollutant Emission Factors* (for both stationary and mobile sources) (USEPA, 1995e, 1996d, 1997d, 2000h), as well as many other documents and software.

EPA's Support Center for Regulatory Air Models (SCRAM) website (www.epa.gov/ttn/scram/) provides extensive information on the models discussed in *Guideline on Air Quality Models* (USEPA, 1999e), including downloadable software and users guides for many of the models.

The Ambient Monitoring Technology Information Center (AMTIC) website (www.epa.gov/ttn/amtic/) contains information on monitoring programs and methods and other monitoring-related information.

The umbrella website for all three of the above is the Technology Transfer Network (www.epa.gov/ttn/), which also has other useful information and links in addition to those noted above.

Sources for land and waste-related activities:

EPA's Office of Solid Waste and Emergency Response has compiled an extensive catalog summarizing their publications (USEPA, 2000i). It has also published a "peer review draft" document titled *Human Health Risk Assessment Protocol for Hazardous Waste Combustion Facilities* (USEPA, 1998j), which deals with how to assess risks from hazardous waste incinerators. These reports are available on-line.

Chemical accidents and transportation-related spills:

Assessing an accidental chemical release exposure involves several steps. The typical analytical steps in the overall assessment are process analysis, likelihood or frequency of accidents, source term modeling, dispersion or consequence modeling, and the exposure assessment.

- The *process analysis* is a formal, systematic analysis of the process where a chemical is handled to determine the probabilities and consequences of acute, catastrophic failures of engineered systems leading to an accidental release of the chemical. This analysis is often called a process hazards analysis (PHA). Several formal PHA evaluation techniques are available, including "What-If," "Failure Mode and Effect Analysis," "Event-Tree," and "Fault-Tree" analyses (USEPA, 1998e; AIChE, 1992).

- The *likelihood or frequency of accidents* step is an evaluation of each of the scenarios uncovered in the process analysis step for likelihood or frequency of occurrence.

- *Source term modeling*, which estimates the amount or rate of release in case of accident, is performed once the failure scenarios are determined. A wide variety of published calculation methods or models are available (USEPA, 1998e, 1999d) to determine the source terms for an accidental chemical release.

- *Dispersion or consequence modeling* is performed once the source terms (rate and duration of the release) are known. A wide variety of dispersion and consequence modeling tools, ranging from simple screening models to sophisticated and complex computer applications, are available for this step (USEPA, 1993a, 1999d; AIChE, 1996). In addition to the source terms generated above, several other data elements are needed, such as physical/chemical properties (e.g., whether the vapor cloud is heavier than air or water reactive), meteorological conditions (e.g., wind speed and direction, temperature, humidity), and terrain surrounding the facility (e.g., buildings or valleys that may channel or disperse a vapor cloud). Physical/chemical properties can be found in chemical reference texts such as *Kirk-Othmer's Encyclopedia of Chemical Technology* (Kroschwitz and Howe-Grant, 1994), *Perry's Chemical Engineers' Handbook* (Perry et al., 1997), on Material Safety Data Sheets (MSDS)[18], or *Risk Management Guidance for Offsite Consequence Analysis* (USEPA, 1999d). Meteorological conditions are often collected on-site or at local airports. Information about terrain can be collected from topological maps or by visual inspection. Guidance on all these parameters is available in USEPA (1999d).

[18] There are many searchable MSDS databases on-line that can be located with most search engines.

- The final step is the *exposure assessment*, which is related to, and builds from, the dispersion or consequence modeling step. The dispersion or consequence modeling depends on a health endpoint and the exposure level related to that endpoint. Besides lethality, concentrations for certain health effects (e.g., odor thresholds, eye irritation) are available for several common toxic substances (NIOSH, 1997; ACGIH, 1998; AIHA, 2000).

B.2. Resources Relevant to Exposures to Nonchemical Stressors

Biological stressors:

The International Life Sciences Institute's Risk Science Institute has published a workshop report entitled "Revised Framework for Microbial Risk Assessment" (ILSI, 2000), which looks at methods for assessing risks to microorganisms such as *Cryptosporidium*, which has caused disease outbreaks when it contaminates drinking water. The methodology is superficially similar to that of a risk assessment conducted for a chemical pollutant, but only at the most general level. For example, the characterization of exposure in the ILSI framework differs from that in an environmental chemical exposure assessment; it includes (1) pathogen characterization, (2) pathogen occurrence, (3) exposure analysis, and, finally, developing (4) an exposure profile.

Radiological stressors:

EPA's Office of Air and Radiation maintains a web page at <http://www.epa.gov/radiation/assessment/>. This page provides (or cites) much of the needed documentation for performing risk assessments for radionuclides, including *Radiation Exposure and Risk Assessment Manual (RERAM)* (USEPA, 1996e) and several Federal guidance reports (USEPA, 1988, 1993d, 1999l).

Noise, vibration, and congestion:

The U.S. Department of Housing and Urban Development (HUD) has issued *The Noise Guidebook* (HUD, 1991), which implements the existing noise regulations (24 CFR 51-B) and includes the HUD noise assessment guidelines. (The guidebook is available in hard copy only.)

The Federal Railroad Administration has developed a manual titled *High-Speed Ground Transportation Noise and Vibration Impact Assessment* (DOT, 1998), which provides the theory, equations, and applications of noise and vibration analysis for high-speed railroads. Much of the theory and information is also applicable to other noise and vibration problems. Appendix A of the DOT guide is a general discussion of noise concepts, with references. The guide is available on-line (http://project1.parsons.com/ptgnechsr/noise_manual.htm).

The National Institute of Occupational Health and Safety has done much research on the interaction of noise with chemical exposures (Morata, 2000).

Odor:

EPA's Office of Wastewater Management has issued a report titled *Guide to Field Storage of Biosolids* (USEPA, 2000j), which contains an appendix on "Odor Characterization, Assessment, and Sampling." Odor assessment is an analytic-deliberative process involving both science-based analytical methods and more subjective analysis. The appendix of the guide discusses sensory characterization of odors (character, intensity, pervasiveness, quantity), some practical options for assessing odors in a community, and the chemistry of odors (including range of odor thresholds). It also discusses odor sample collection and analysis and has several dozen references for further information. This report is available on-line (www.epa.gov/owm/bio/fsguide/).

APPENDIX C: SOME THOUGHTS ON BACKGROUND EXPOSURES[19]

When looking at aggregate exposures or cumulative risks of citizens, "background exposures" to specific chemicals are no less "real" than the exposures to pollution usually studied for regulatory purposes. Whereas in historical single-chemical assessments conducted for limiting pollution, background sources of the chemical were often irrelevant to the questions being asked of the assessment (or ignored as having negligible effect on risk), background sources in cumulative risk assessments are rarely irrelevant.[20]

Background concentrations can be categorized as either *naturally occurring*, that is, chemicals that are naturally present in the environment before it was influenced by humans, or *anthropogenic*, that is, present in the environment due to historical human-made sources. Naturally occurring background chemicals may be either localized or ubiquitous. Anthropogenic background sources can be either localized from a point source or generalized from unidentified sources or nonpoint sources.

Assessments of morbidity incidence and death rates, market basket surveys, and pesticide residue surveys also provide information that can be reflective of background chemical concentrations as well as overt pollution. Background issues extend across all media, beyond regulated sources, and beyond direct exposure. Many chemicals are naturally present in the environment (e.g., soils, water, vegetation, and other biota) and are consequently part of dietary, dermal, and inhalation exposures. In some cases, naturally occurring substances may be present at levels that exceed health-based or risk-based regulatory standards (e.g., drinking water standards) or other levels established to protect human health and the environment. Because cumulative risk assessments are population based, exposures due to naturally occurring background concentrations should typically be considered important.

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[19] Several terms are used to discuss background, and there are several ways to describe different aspects of this issue. It has been suggested (deFur, 2002) that a more appropriate term for present conditions is "ambient," and that "background" should be reserved for some untouched, even pristine state or condition. Although the Technical Panel discussed this use of the word "background" as a pristine reference area, the discussion in this appendix is meant to more closely reflect the way the word is used in practice within EPA. It is acknowledged that not all programs or scientists even within EPA use this term to mean the same thing.

[20] The word "background" is often used to describe exposures to chemicals or other stressors that derive from sources other than the sources being assessed. For example, in the Agency's assessment of residual risk associated with hazardous air pollutant emissions from particular categories of sources that remain after the implementation of technology-based controls, "background" is defined as all hazardous air pollutant exposures (via inhalation or other routes) not associated with the source(s) being assessed. At a Superfund site, "background contamination" refers to contamination that is not related to the site release of chemicals, as defined by *Comprehensive, Environmental Response, Compensation and Liability Act* (CERCLA) (P.L. 96-510, December 11, 1980, as amended by P.L. 98-802, August 23, 1983, and P.L. 99-499, October 17, 1986). Such focusing or segregation in a risk assessment can be useful to decisions involving pollution sources covered by particular statutory authorities, but it is typical of a chemically focused assessment rather than a population-focused assessment such as a cumulative risk assessment.

There are several important issues related to natural or anthropogenic background concentrations in cumulative risk assessment. First, if the risks posed by background concentrations of certain chemicals are significant (and some may approach or exceed health reference levels), their exclusion from the cumulative risk estimates and characterization may seriously distort the portion of the total estimated risk thought to be posed to the population by a specific evaluated source. A second issue is the problem of whether background chemical exposures can be clearly distinguished from specific source-related chemicals and how to quantify these exposures. It may be important in a cumulative risk assessment to estimate background exposures separately from specific source-related exposures, so that the risk assessor can provide the community with a more complete picture of both total and known source-related risks. This also provides a clearer, more complete picture for making risk management decisions. Finally, there may be problems in identifying representative geographic areas for determining background levels for comparison.

Finally, background exposures for a community or population may also include both voluntary and involuntary exposures and subsequent risks. Involuntary exposures are associated with the naturally occurring or anthropogenic background concentrations described above. Voluntary exposures, such as are associated with lifestyle decisions, are exposures due to activities such as smoking, consuming char-grilled meats with polycyclic aromatic hydrocarbons, or other choice-based exposures and may also sometimes be defined in the assessment as background exposures if they are not assessed directly in the cumulative risk assessment.

APPENDIX D: EXAMPLES OF OUTLINES OF ANALYSIS PLANS[21]

D.1. Outline for Human Health Analysis Plan for Pesticides Under the 1996 Food Quality Protection Act (FQPA)

Risk management/regulatory goal: Protection of the general human population and susceptible subpopulations to adverse effects from exposure to pesticide "X" under FQPA.

Assessment Endpoints:

- human or animal health status of exposed versus unexposed populations/cohorts/dose groups

Measures of Effects:

- general types of toxicological effects grouped according to acute, subchronic, and chronic exposure durations
- organ-specific toxicity such as reproductive effects, developmental effects, neurotoxicity, developmental neurotoxicity, immunotoxicity, hepatotoxicity, pulmonary effects, cardiovascular effects, etc.
- general classes of toxic effects such as carcinogenicity, mutagenicity

Measures of Exposure:

- monitoring of food, water, residential, occupational exposures, etc. (direct or surrogate)
- monitoring of biological fluids or biomarkers (blood, urine, DNA or other macromolecules)

What Can and Cannot Be Done Based on Planning and Scoping

- pathways and relationships to be evaluated
- resource restraints
- milestones for completion of risk assessment

Methods for Conducting Risk Analysis

- RfD
- margin of exposure
- probabilistic risk assessment based on dose-response or exposure parameters
- quotients (e.g., ratio of exposure level to toxicity threshold)
- narrative discussions
- other considerations (e.g., mechanisms of action, toxicokinetic models, timing of dose, sensitive population characteristics)

Data Needs and Uncertainties

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[21] Conceptual models are not included here.

D.2. Outline for Ecological Analysis Plan

Risk management/regulatory goal: Viable, self-sustaining coho salmon population that supports a subsistence and sport fishery.

Assessment endpoints: Coho salmon breeding success, fry survival, and adult return rates.

Measures of Effects:

- egg and fry response to low dissolved oxygen
- adult behavior in response to obstacles
- spawning behavior and egg survival with changes in sedimentation
- population data over time in relation to fish passage

Measures of Ecosystem and Receptor Characteristics:

- water temperature, water velocity, and physical obstructions
- abundance and distributions of suitable breeding substrate
- abundance and distribution of suitable food sources for fry
- feeding, resting, and breeding behavior
- natural reproduction, growth, and mortality rates

Measures of Exposure:

- number of hydroelectric dams and associated ease of fish passage
- toxic chemical concentrations in water, sediment, and fish tissue
- nutrient and dissolved oxygen levels in ambient waters
- riparian cover, sediment loading, and water temperature

What Can and Cannot Be Done Based on Planning and Scoping

- pathways and relationships to be evaluated
- resource restraints
- milestones for completion of risk assessment

Methods for Conducting Risk Analysis

- quotients
- narrative discussions
- stressor-response curves with probabilities

Data Needs and Uncertainties

APPENDIX E: TOXICOLOGIC SIMILARITY—ORGANOPHOSPHORUS PESTICIDES

The Food Quality Protection Act of 1996 (FQPA) requires that EPA reassess pesticide tolerances (legal limits for residues in food) that were in effect as of August 1996. As part of the reassessment, EPA should consider available information concerning the cumulative effects on human health resulting from exposure to multiple chemicals that have a common mechanism of toxicity. In this context, pesticides are determined to have a common mechanism of toxicity if they produce the same toxic effect in the same organ or tissue by essentially the same sequence of major biochemical events (USEPA, 1999h).

Shortly after enactment of FQPA, EPA began developing new methods and tools that would allow the consideration of combined risks from exposure to several pesticides via several pathways and routes of exposure. Actual data sets for organophosphorus (OP) pesticides were used in pilot analyses to test these methods. The methods and pilot analyses were subjected to peer review through the FIFRA Scientific Advisory Panel to ensure the use of sound science. As part of this ongoing effort, on December 28, 2001 EPA's Office of Pesticide Programs (OPP) announced the availability of the preliminary organophosphorus cumulative risk assessment [66FR67249-67250]. The risk assessment is available electronically at <http://www.epa.gov/pesticides/cumulative>. In preparing the cumulative risk assessment for the OP pesticides, OPP followed five major steps.

1. *Selection of the specific pesticides, pesticide uses, and pathways and routes of exposure to include in the quantitative analysis.*

The selection of the specific OP pesticides began with identifying a "common mechanism group." This was accomplished following *Guidance For Identifying Pesticide Chemicals And Other Substances That Have A Common Mechanism Of Toxicity* (available at http://www.epa.gov/pesticides/trac/science). All 39 registered OP pesticides share inhibition of acetylcholinesterase as a common mechanism for causing adverse effects (USEPA, 1998k).

The common mechanism group was further refined to reflect current use patterns and information on the detection of residues from USDA's Pesticide Data Program. This resulted in the following recommendations for quantitative analysis: include 22 OP pesticides for the food pathway of exposure; 24 OPs for the water pathway and 10 OPs for residential exposures were identified on the basis of use patterns and their individual assessments.

2. *Dose-response analysis for toxic potencies, relative contribution from each OP pesticide, and selection of an index chemical to use as the point of reference in the dose-response analysis.*

To determine the combined risk from multiple OP pesticides, EPA used the relative potency factor approach (for additional examples of comparative potency approaches, see Albert et al., 1983; Lewtas, 1985, 1988). The index chemical was selected on the basis of the quality of the dose-response data. Then the relative potency of each OP pesticide was estimated by taking the ratio of its toxic potency to that of the index chemical.

In selecting studies for evaluating toxic potencies, EPA used relative potency factors and points of departure developed from cholinesterase inhibition in rats exposed to pesticides for 21 days or more. This practice was adopted to reflect cholinesterase inhibition at a point in the treatment schedule at which a steady state had been achieved. OPP elected to use data that reflected a steady state in the interest of producing relative potency factors that are reproducible and reflect less uncertainty due to rapidly changing time-sensitive measures of cholinesterase.

Also, EPA considered that people generally have some level of prior exposure to OP pesticides. Further, the effects of exposure can persist for several days to weeks. Therefore, people may be more vulnerable to subsequent exposures to OP pesticides than might be predicted if these prior exposures are not considered.

3. *Estimation of the risks associated with all pertinent pathways of exposure in a manner that is both realistic and reflective of variability due to differences in location, time, and demographic characteristics of exposed groups.*

Evaluation of the OP pesticide use profiles allowed for the identification of exposure scenarios that may overlap, co-occur, or vary between chemicals. In addition, the use of profiles allowed for the identification of populations of potential concern. On the basis of this analysis, EPA considered exposure to OP pesticides in food to be uniform across the nation (i.e., there are no significant differences in food exposure due to time of year or geographic location). For the residential and drinking water pathways of exposure, EPA divided the nation into 12 regions for assessment. This allowed for the consideration of such factors as the location of vulnerable surface watersheds and region-specific pest pressures. To estimate risks, EPA used Calendex, a calendar-based computer model. This model integrates the various pathways of exposure while simultaneously incorporating the time dimensions of the data. The model produces a detailed profile of the potential exposure to individuals across a calendar year.

4. *Identification of the significant contributors to risk.*

Although interpretation of the preliminary organophosphorous cumulative risk assessment is ongoing, there are some early indications concerning contribution to risk. The drinking water pathway for exposure does not appear to be a major contributor to the

total cumulative risk. Residential exposure appears to be a contributor to risk, particularly inhalation exposures from certain no-pest strips and crack and crevice treatments. Childhood exposure from mouthing hands also appears to be a contributor, but there is a great deal of uncertainty associated with the estimates.

5. *Characterization of the confidence in the results and the uncertainties encountered.*

In addition to some uncertainties noted above, EPA identified many areas for additional analysis, including sensitivity analyses on input parameters, verification of residential use patterns, closer examination of the tails of the food consumption distribution, and evaluation of the effect of assumptions about residue concentrations in baby foods.

APPENDIX F: OTHER TYPES OF CUMULATIVE ASSESSMENTS

Several other types of cumulative assessments are related to the types of human health and ecological cumulative assessments done by the Agency. It is beyond the scope of this framework to discuss these in detail, but a short explanation of several other types of cumulative assessments are given in this appendix.

F.1. Quality-of-Life Assessments

One type of assessment that resembles a cumulative risk assessment—but whose evaluation may require a different approach from the traditional National Research Council risk paradigm—is the quality-of-life assessment. These assessments define "harm" to an individual or community broadly, then evaluate the importance of the various threats of harm to a set of "quality-of-life" criteria. These assessments do not usually attempt to predict probability that the harm will occur (as would a cumulative risk assessment), but rather aim to apply the community's values to deal with the most important perceived threats.

Although a quality-of-life assessment is not a risk assessment in most cases, changes in quality-of-life factors may affect the vulnerability of a population to health or ecological risks and consequently may be part of the considerations in a cumulative risk assessment. Because few, if any, established and accepted relationships are currently available quantitatively linking quality-of-life factors and health or ecological risk, this is an area in which further research may prove valuable.

To evaluate the effects on human or ecological health from these types of impacts, a more deliberative approach (in the analytical-deliberative process) is needed than is used in, say, cancer risk analysis. To better help characterize these impacts, EPA's *A Guidebook to Comparing Risks and Setting Environmental Priorities* (USEPA, 1993b) suggests a six-step process in quality-of-life analysis:

1. Identify impacts and determine the values of the community.
2. Identify and define evaluative criteria.
3. Collect and analyze data on impacts.
4. Characterize impacts for all problem areas.
5. Present findings and rank problem areas for quality-of-life impacts.
6. Analyze future environmental conditions and risk management considerations.

Vermont's Quality-of-Life Criteria

Impacts on Aesthetics: Reduced visibility, noise, odors, dust and other unpleasant sensations, and visual impact from degradation of natural or agricultural landscapes.

Economic Well-Being: Higher out-of-pocket expenses to fix, replace, or buy items or services (e.g., higher waste disposal fees, cost of replacing a well, higher housing costs), lower income or higher taxes paid because of environmental problems, and health-care costs and lost productivity caused by environmental problems.

Fairness: Unequal distribution of costs and benefits (e.g., costs and benefits may be economic, health-related, aesthetic).

Future Generations: Shifting the costs (e.g., economic, health risks, environmental damage) of today's activities to people not yet able to vote or not born yet.

Peace of Mind: Feeling threatened by possible hazards in air or drinking water or potentially risky structures of facilities (e.g., waste sites, power lines, nuclear plants), and heightened stress caused by urbanization, traffic, etc.

Recreation: Loss of access to recreational lands (public and private) and degraded quality of recreation experience (e.g., spoiled wilderness, fished-out streams).

Sense of Community: Rapid growth in population or number of structures or development that changes the appearance and feel of a town; loss of mutual respect, cooperation, ability, or willingness to solve problems together; individual liberty exercised at the expense of the community; the loss of Vermont's landscape and the connection between the people and the land.

Source: State of Vermont, 1991

Quality-of-life impacts are determined by analyzing a set of criteria developed for each community, depending on what it values. Stressors are those things that threaten to degrade the quality-of-life criteria for that community. An example of a set of quality-of-life criteria and their descriptions is shown in the box on this page. These criteria were developed by the State of Vermont's Agency of Natural Resources (State of Vermont, 1991). Vermont's experience in evaluating these criteria was described as a qualitative description of harm or, in their terms, "risk":

> Because most of these seven criteria are intangible, they are extremely difficult to measure or quantify. The Quality-of-Life Work Group described how each problem area affects each criterion and how widespread or intense the effects are. Although these non-quantitative descriptions of risk often lack precision and scientific objectivity, they focus attention on specific critical issues and thus are useful tools for comparing the problems systematically and consistently. (State of Vermont, 1991)

Quality-of-life issues can encompass much more than the criteria shown in the example and thus may introduce much additional complexity into the analysis. For instance, there may be feedback loops that cannot be easily evaluated, for example, loss of property value or aesthetics tends to negatively affect the socioeconomic system, which tends to increase rates of crime, traffic accidents, and communicable pathogen transmission, all of which in turn ultimately reflect on overall community health or ecological risk. Some cumulative risk assessments may consequently include quality-of-life impacts as indirect measures of health effects if sufficient links can be established between the two.

F.2. Cumulative Impact Assessments

The National Environmental Policy Act (NEPA) defines "cumulative impact" (see box), and has certain requirements for a cumulative impacts analysis. Although the Council on Environmental Quality's guidelines for cumulative impact analysis (CEQ, 1997) take a primarily qualitative approach to the analysis, this is a multiple-stressor, multiple-effect analysis that looks at a variety of impacts on the environment.

The projects or actions that NEPA addresses can be viewed as sources of stressors. Under NEPA, a description of the affected environment in an environmental impact assessment contains four types of information: (1) data on the status of important natural, cultural, social, or economic resources and systems; (2) data that characterize important environmental or social stress factors; (3) a description of pertinent regulations, administrative standards, and development plans; and (4) data on environmental and socioeconomic trends. Health effects on populations and susceptible individuals are part of the affected environment as considered by the NEPA cumulative effects analysis, but the NEPA analysis may also consider effects on historic and archaeological resources, socioeconomic factors such as employment, human community structure, and quality of life changes.

Although there is not always a clear relationship between these NEPA cumulative impacts and effects relevant to human health, the NEPA methods and tools for cumulative impact analysis may be useful for cumulative risk assessments. For example, cumulative impact analysis begins with an extensive scoping process and relies on conceptual models to plan the analysis. NEPA effects data may help risk assessors identify susceptible subpopulations, environmental pathways, or exposure patterns.

EPA Region 6 has developed a system called the Cumulative Risk Index Analysis (CRIA), primarily for NEPA-type assessments (Osowski et al., 2001). The CRIA contains some 90 criteria with which to evaluate the health of an area and its ecosystem/human populations. These criteria help evaluate such diverse factors as human health, ecosystem health, and environmental justice considerations. Each criterion, which leads to an indexing of 1 through 5, has been through the deliberative process and peer review and is well documented.

We also acknowledge that other Federal agencies have been preparing "cumulative risk analyses" for various

NEPA's "Cumulative Impact" Definition

Council on Environmental Quality Regulation 1508 for Implementing the *National Environmental Policy Act* of 1969 [P.L. 91-190, 42 U.S.C. 4321-4347, January 1, 1970, as amended by P.L. 94-52, July 3, 1975, P.L. 94-83, August 9, 1975, and P.L. 97-258, §4(b), Sept. 13, 1982] defines "cumulative impact" as "the impact on the environment which results from the incremental impact of the action when added to other past, present, and reasonably foreseeable future actions regardless of what agency (Federal or non-Federal) or person undertakes such other actions. Cumulative impacts can result from individually minor but collectively significant actions taking place over a period of time."

Source: CEQ, 1997

purposes related to their own mission as part of environmental impact statements (e.g., NOAA, 1999).

F.3. Empirically Derived Medical Models

The medical profession has long used empirically derived models to predict the chances of particular health effects in individual patients. In this approach, the characteristics of individuals within the population are correlated with the incidence of specific diseases or effects. For example, the risk factors for stroke are increasing age, heredity (family history) and race, prior stroke, high blood pressure, cigarette smoking, diabetes mellitus, carotid and other artery disease, heart disease, transient ischemic attacks, high red blood cell count, sickle cell anemia, socioeconomic factors, excessive alcohol consumption, and certain types of drug abuse (American Heart Association, 2000). Each of these risk factors can be correlated with stroke incidence, and then the risk of stroke from various combinations of these factors can be explored. In this way, the analysis is "cumulative," but "risk factors" are not always synonymous with "stressors."

Physicians use models containing effect-specific risk factors to advise patients of the probabilities of future effects (e.g., stroke, breast cancer) on the basis of their medical history. Although the medical data upon which these factors are based have been well developed for many effects in humans, there are substantial data gaps in terms of the role played by exposures to many chemicals in the environment in the development of human disease. This empirically derived medical model approach to cumulative risk may be built on links between risk factors and effects for better-studied stressors but may be limited or nonexistent for less robust health effects databases. Although this approach may some day be applicable to human health and environmental risk assessment such as EPA conducts, at present the data and methods are not available.

In a larger sense, although empirically derived models may be cumulative risk models, the approach to determining risk is substantially different from the risk assessment approach used by EPA, where a combined effect is estimated as the *predicted* aggregation of the effects of several different stressors. In an empirical model such as physicians use, the focus is on an effect of concern, and the model derives the influence of various "stressors" or "risk factors" from actual observations, usually through the use of multiple regression analyses. Although ideally the equations derived to represent the influences of various factors on the measured outcome (the effect of concern) would be causal-predictive models, in practice they are usually the most parsimonious "best fit" equations that satisfy statistical criteria. The versatility of this approach, however, is the ability to tease apart contributions of different sources of environmental exposures of interest. This is illustrated by Laden et al. (2000) in the association of particulates from different sources with short-term mortality changes. This approach also has considerable potential to be used in conjunction with biomarkers as dependent variables (Hattis, 2002).

The topic of cumulative risk models will likely be covered in more detail in the future guidelines for cumulative risk assessment.

F.4. Risk Surrogates

Geographic information systems and related mapping techniques (see, e.g., Environmental Defense, 2001) appear to hold some promise as tools for presenting integrated information concerning cumulative risks without mathematically combining disparate measures. Considerable methods development work remains to be completed.

Not all statements of probability of harm are expressed as probabilities of specific health effects. Cohen (1991) uses mortality ratios to derive "loss of life expectancy" (LLE) estimates for a wide variety of risk-related activities. For example, workers in all occupations have a 60-day LLE as a result of working, but workers in agriculture have a 320-day LLE and construction workers a 227-day LLE as a result of their particular occupation. These types of statements are empirically derived, probability-based statements of harm that do not use "probability of adverse health effect" as the basis for the risk statement. For estimates such as LLEs, one could theoretically add up the various activities and the corresponding LLEs in days to estimate a cumulative risk in terms of loss of life expectancy. These "other" types of risk-surrogate probability statements could conceivably be used in cumulative risk assessment, although currently they are not widely used, perhaps due to lack of methods.

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