REVIEW DRAFT

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Framework for Cumulative Risk Assessment

IMPORTANT NOTICE:

This document does not represent official Agency policy and, therefore, is not for citation or quotation. It is a work-in-progress developed by the Cumulative Risk Assessment Technical Panel of the Risk Assessment Forum and may provide a basis for development of an Agency-wide *Framework for Cumulative Risk Assessment.* This draft is being provided for the purpose of external peer consultation.

The mention of commercial products is for illustration only and in no way implies EPA endorsement of these products.

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Acknowledgments [to be completed later]

Foreword [to be completed later]

Several reports have highlighted the importance of understanding the accumulation of risks from multiple environmental stressors. These include the National Research Council's 1994 report *Science and Judgment in Risk Assessment* and the 1997 report by the Presidential/Congressional Commission on Risk Assessment and Risk Management entitled *Risk Assessment and Risk Management in Regulatory Decision-Making*. In addition, legislation such as the *Food Quality Protection Act of 1996*, has directed the Environmental Protection Agency to move beyond single chemical assessments and to focus, in part, on the cumulative effects of chemical exposures occurring simultaneously. Further emphasizing the need for EPA to focus on cumulative risks are cases filed under Title VI of the *1964 Civil Rights Act*. These cases have emphasized the need for a population-based approach to assessing human health risks from environmental contaminants.

In response to the increasing focus on cumulative risk, several EPA programs have begun to explore cumulative approaches to risk assessment. In 1997, The EPA Science Policy Council issued a guidance on planning and scoping for cumulative risk assessments (http://www.epa.gov/ORD/spc/2cumrisk.htm). More recently, the Office of Pesticide Programs has developed draft cumulative risk assessment guidance focused on implementing certain provisions of FQPA. The Office of Air Quality Planning and Standards has applied cumulative exposure models in its analyses for the National-Scale Air Toxics Assessment (NATA). In addition, community-specific cumulative risk assessment has been explored through the Agency's Cumulative Exposure Project.

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. 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.

[This preliminary draft of the Framework for Cumulative Risk Assessment is being made available at this time for the purpose of peer consultation. At the completion of the peer consultation process, the document will be revised and then reviewed by the Agency's Science Advisory Board (SAB). The final framework document will reflect the SAB comments and will require review and approval by the Agency's Science Policy Council.]

William P. Wood
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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. This is underscored by recent reports such as the National Research Council's 1993 report *Pesticides in the Diets of Infants and Children,* (NRC, 1993) the 1994 NRC report *Science and Judgment in Risk Assessment,* (NRC, 1994), the 1995 National Academy of Public Administration report *Setting Priorities, Getting Results* (NAPA, 1995), the 1997 report by the Presidential/Congressional Commission on Risk Assessment and Risk Management titled *Risk Assessment and Risk Management in Regulatory Decision-Making* (PCCRARM, 1997), and the EPA Science Advisory Board report *Toward Integrated Environmental Decision-Making* (USEPA, 2000a). There also have been several recent pieces of legislation that mandate the 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 non-occupational pathways of exposure.

Assessment of cumulative risk through complex exposures is one of the high priorities of the Agency, especially in light of FQPA mandates, and 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. This Framework is meant to lay out broad areas where analysis might be done 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 done 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.

According to the expert panel report *Safeguarding the Future: Credible Science, Credible Decisions* (USEPA 1992a), a key role of science at EPA is to reduce uncertainties in environmental decision-making. The report points out that while EPA historically has 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. In *Pesticides in the Diets of Infants and Children,* (NRC, 1993) the NRC 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 with a common toxic effect. Further, the report identifies important differences in susceptibility with age. NRC in *Science and Judgment in Risk Assessment* (NRC, 1994) states 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 report recommended that EPA assess risks to infants and children whenever it appears that their risks might be greater than those of adults. Public criticisms documented in this report note that EPA does not often consider the possibility of synergistic interactions when multiple chemical exposures occur, nor does it 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. Finally, the FQPA [P.L.104-170, August 3, 1996], requires research on the influence of complex exposures on non-cancer human health effects of pesticides and other toxic substances.

The issue of 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, USEPA 1998a).

There are over 20,000 pesticide products on the market (USEPA, 2001d), and over 80,000 existing chemicals on the TSCA inventory (USEPA, 2001e). Each year, an additional number of chemicals are added. The question of how to assess the cumulative effect of these chemicals on the population will be a great challenge to the Agency in the coming decade. This issue may well become the primary issue in the risk assessment field in the next ten years.

Authors, Contributors, and Reviewers [to be completed]

List of Abbreviations and Acronyms

ACGIH	- American Conference of Government Industrial Hygienists
AFS	- AIRS Facility Subsystem
AIChE	- American Institute of Chemical Engineers
AIHA	- American Industrial Hygiene Association
AIRS	- Aerometric Information Retrieval System
AMTIC	- Ambient Monitoring Technology Information Center
APCA	- American Crop Protection Association
APEX	- Air pollution exposure model
ARE	- Acute reference exposure
ATSDR	- Agency for Toxic Substances and Disease Registry
CARES	- Cumulative and Aggregate Risk Evaluation System
CBEP	- Community-based environmental protection
CEQ	- Council for Environmental Quality
CFR	- Code of Federal Regulations
CHIEF	- Clearinghouse for Inventories and Emissions Factors
COHb	- Carboxyhemoglobin
CRIA	- Cumulative Risk Index Analysis
DALY	- Disability-adjusted life year
DOT	- United States Department of Transportation
EPA	- United States Environmental Protection Agency
FIFRA	- Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	- Food Quality Protection Act
GAO	- United States General Accounting Office
GIS	- Geographical Information System
HAP	- Hazardous air pollutant
HEC	- Human equivalent concentration
HRS	- Hazard Ranking System
HUD	- United States Department of Housing and Urban Development
IED	- Integrated Environmental Decision-making
ILSI	- International Life Sciences Institute
LADD	- Lifetime average daily dose
LDP	- Locational Data Policy
LLE	- Loss of life expectancy
LOAEL	- Lowest observed adverse effect level
MOE	- Margin of exposure
MSDS	- Materials Safety Data Sheet
NAAQS	- National Ambient Air Quality Standards
NAPA	- National Academy of Public Administration
NATA	- National-Scale Air Toxics Assessment
NEPA	- National Environmental Policy Act

NHEXAS	- National Human Exposure Assessment Survey
NIOSH	- National Institute for Occupational Safety and Health
NOAEL	- No observed adverse effect level
NRC	- National Research Council
OAR	- Office of Air and Radiation (EPA)
OECA	- Office of Enforcement and Compliance Assurance (EPA)
OPP	- Office of Pesticide Programs (EPA)
OPPTS	- Office of Prevention, Pesticides, and Toxic Substances (EPA)
ORD	- Office of Research and Development (EPA)
OSWER	- Office of Solid Waste and Emergency Response (EPA)
P.L.	- Public Law
PAH	- Polycyclic Aromatic Hydrocarbon
PCB	- Polychlorinated biphenyl
PCS	- Permit Compliance System
PM-10	- Particulate matter of 10 micrometer size or less
pNEM	- Probabilistic NAAQS Exposure Model
QALY	- Quality-adjusted life year
RfC	- Reference Concentration
RfD	- Reference Dose
SAB	- Science Advisory Board
SAP	- Science Advisory Panel
SAR	- Structure-activity relationship
SCRAM	- Support Center for Regulatory Air Models
SHEDS	- Stochastic Human Exposure and Dose Simulation model
SPC	- Science Policy Council
TEAM	- Total Exposure Assessment Methodology
TEMRAP	- The European Multi-Hazard Risk Assessment Project
TIA	- Transient ischemic attack
TRI	- Toxic(s) Release Inventory
TRIM.Expo	- Total Risk Integrated Methodology, exposure module
U.S.C.	- United States Code
UF	- Uncertainty factor
USEPA	- United States Environmental Protection Agency

Executive Summary [to be completed last]

1. INTRODUCTION

During much of its early history, EPA focused its efforts on cleaning up the overt pollution problems of the 1960s and 1970s. Until EPA was established in 1970, relatively uncontrolled air emission, water effluents, and dumping of wastes had led to pollution of the environment that was easily detected by the five senses. The most effective and efficient way to approach these overt problems of the 1970s was to find the entry point of the pollution into the environment, and to keep it from entering the environment by controlling it there. Looking back, we see a strategy that moved to control stack emission, industrial and municipal effluents, pesticide application, land applications, burial of chemical wastes, and other so-called “sources” of pollution. In addition, criteria and standards were established as goals for cleanup of the various environmental media. By the 1980s, this so-called “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, since risk assessments were being used as one of the factors in EPA’s decision-making for regulations to control pollution. The focus on sources led naturally to analysis of what types of pollutants were in effluents, air emissions, and waste sites. These were chemical, biological, and sometimes radiological agents. By the 1970s, the links between some chemicals and certain diseases such as cancer had been established through a series of bioassays, or in the cases of chemicals like vinyl chloride and asbestos, through epidemiological studies. New analytical techniques of the 1970s also made it possible to detect very minute concentrations of chemicals for the first time. 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.

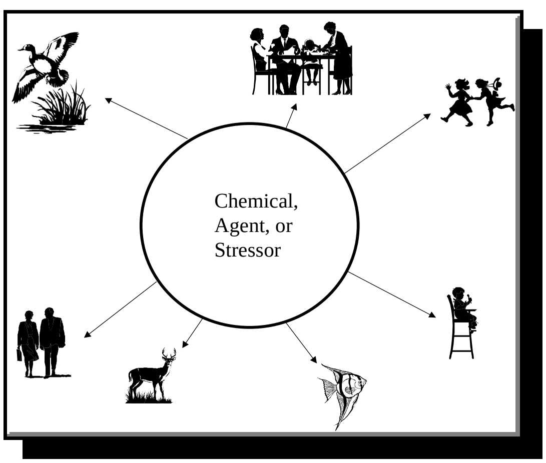

Figure 1. Chemical (or stressor) focused assessment starts with a source and evaluates how the chemical gets to various populations or ecological targets. Individual assessments may choose to pursue some or all pathways, media, or population segments.

Risk assessment methodology of the 1970s and early 1980s, for this reason, tended towards single chemical assessments (see Figure 1). The

1983 National Research Council report *Risk Assessment in the Federal Government* (NRC, 1983) was largely focused on the single chemical risk assessment approach when it spoke of the four parts of a 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), were also largely focused on single chemical assessment.

Research done or sponsored by EPA in the early 1980s, however, was taking the first steps toward a different type of risk assessment methodology, one that focused on the persons exposed rather than the chemicals (Figure 2). The goals of this second, population-based, approach were much more useful to decision-makers who were focusing on public health or ecological health questions, rather than controlling sources of pollution. The approach for the chemical-focused and population-focused approaches depicted in the two figures are quite different, even though some of the tools to do the assessment may be the same.

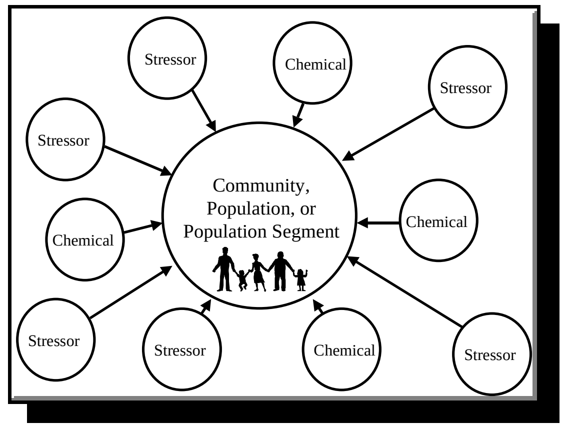

Figure 2. Population-based assessments start with the receptors, and determine what chemicals, stressors, or other risk factors are affecting them.

The challenges posed by the population-based assessment can be daunting. Taken to the extreme, Figure 2 represents a concept of "total risk" for the population or population segment being evaluated, with each chemical, biological, radiological, or other stressor 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 developing a way to add up all the risks among stressors across a population of individuals with different exposures, susceptibilities, etc. 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 led to a larger study, the National Human Exposure Assessment Survey (NHEXAS) in the 1990s (Sexton, et, al. 1995). Both TEAM and NHEXAS were population-based exposure assessment approaches which developed analytical tools and methodologies to do this type of exposure assessment.

Also in the early 1980s, some progress was being made toward the question of how to add the risks from different chemicals or stressors. The 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. The work on this guidance has continued most recently with a draft chemical mixtures guidance document (USEPA, 2001a) which expands and supplements the 1986 beginnings.

About the same time the Agency made some progress 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, eleven Chicago-area community groups joined together 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 which 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; Lee, 1987). This series of community-based actions, chronicled in the 1990 book *Dumping in Dixie: Race, Class and Environmental Quality* (Bullard, 1990) eventually became known as the Environmental Justice movement. The issues raised by the Environmental Justice movement were the basis of a 1994 Presidential Executive Order [Executive Order 12898, February 11, 1994] which told Agencies, among other things, that "Environmental human health analyses, whenever practicable and appropriate, shall identify multiple and cumulative exposures." In the 1990s, Environmental Justice cases, including the cases which have been filed under Title VI of the *1964 Civil Rights Act*, [P.L. 88-352, July 2, 1964] have added to the demand that a population-based human health risk assessment methodology be developed.

Even before Executive Order 12898 was issued, it was apparent that population-based assessments were going to be needed, in addition to the chemical-based assessments, 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, population-based approach (e.g., NRC 1994). Ecological problems, especially, 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 a part of the 1992 *Framework for Ecological Risk Assessment* (USEPA 1992b) and the 1998 *Guidelines for Ecological Risk Assessment*. (USEPA 1998b)

Also by the early 1990s, it was becoming clear that the population-based assessments being contemplated for EPA's cumulative risk needs and the type of assessments done under the *National Environmental Policy Act* of 1969 (NEPA) were related. 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 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.

The projects or actions that NEPA addresses can be viewed as sources of stressors. Environmental impact assessment under NEPA contains a description of the affected environment that 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. In addition to health effects on populations and susceptible individuals as part of the affected environment, the NEPA cumulative effects analysis would consider effects on historic and archaeological resources, socioeconomic factors like employment, human community structure, and quality of life changes. These may be among the types of effects EPA may be asked to include in future cumulative risk assessments. As EPA moves toward cumulative risk assessment, there is some parallel with the NEPA methods for cumulative impact analysis, which may be applied to cumulative risk assessments.

By the first decade of the twenty-first century, cumulative risk assessment needs have become relatively common, especially in EPA's Regional Offices and in the Office of Civil Rights. Much like the "place-based" ecological assessments, communities are asking for community-based assessments which include human health risk assessments, ecological risk assessments, and sometimes, assessments of "quality of life" factors. It is the demand for population-based human health risk assessments that has driven the need for research into cumulative risk assessment, 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, other regulatory agencies, and other organizations need detailed, comprehensive guidance on methods for evaluating cumulative risk. Before such detailed Agency-level guidance can be 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* will emphasize chemical risks to human health in its discussion, but will do so in the context of the effects from a variety of stressors, including non-chemical stressors. Some important topics that could be characterized as "cumulative risk", such as global climate change, are beyond the scope of this Framework.

With 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 Framework provides wide latitude for planning and conducting cumulative risk assessments in many diverse situations, each based on common principles discussed in the Framework. 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 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 things that are integral to the risk assessment process (but see box at right). These include specific analytical methods, techniques for analyzing and interpreting data, and guidance on issues influencing policy. Rather, on the basis of EPA experience and 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.

EPA's Risk Assessment Guidelines

Carcinogen Risk Assessment (USEPA1986d)
Mutagenicity Risk Assessment (USEPA 1986c)
Chemical Mixtures (USEPA 1986b)
Developmental Toxicity Risk Assessment (USEPA 1991b)
Exposure Assessment (USEPA 1992c)
Reproductive Toxicity Risk Assessment (USEPA 1996b)
Ecological Risk Assessment (USEPA 1998b)
Neurotoxicity Risk Assessment (USEPA 1998e)
Proposed Carcinogen Risk Assessment (USEPA 1996c)

Selected Policy and Guidance Documents

Risk Assessment Guidance for Superfund (USEPA 1989a)
Community Involvement in Superfund RA (USEPA 1999c)
Locational Data Policy (USEPA 1991a)
Framework for Ecological Risk Assessment (USEPA 1992b)
Application of Refined Dispersion Models (USEPA 1993a)
Policy /Guidance for Risk Characterization (USEPA 1995ab)
Handbook for Risk Characterization (USEPA 2000c)
Cumulative Risk Planning and Scoping (USEPA 1997a)
Chemical Emergency Risk Management (USEPA 1998c)
Draft Comparative Risk Framework (USEPA 1998f)
Guideline on Air Quality Models (USEPA 1999a)
Framework for Community Based Env. Prot. (USEPA 1999b)
Guidance for Offsite Consequence Analysis (USEPA 1999d)
Handbook for Peer Review (USEPA 2000b)
Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures (USEPA 2001)
Guiding Principles for Monte Carlo Analysis (USEPA 19997c)

This Framework is meant to lay out broad areas where analysis might be done 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 done 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.

1.2. Intended Audience

The framework 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 who are interested in cumulative risk assessment issues. The style and language used in this Framework document are chosen to be understood by as wide a variety of interested parties as possible, from the policy maker to the risk assessment scientist to the concerned non-scientist member of the general public. It is hoped that this Framework 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[1]

According to common English usage, "cumulative" means (Random House, 1966):

> 1. made up of accumulated parts; 2. increasing by successive additions; 3. tending to prove the same point (e.g., cumulative evidence); 4. additional rather than repeated (e.g., cumulative legacy); 5. taking effect upon completion of another penal sentence (e.g., cumulative sentence); 6. increasing in severity with repetition of the offense (e.g., cumulative penalty); 7. formed by the addition of new material of the same kind (e.g., cumulative book index); 8. summing or integrating overall data or values of a random variable less than or equal to a specified value (e.g., cumulative normal distribution or cumulative frequency distribution)

The key concepts in the definitions are that of *accumulation* (gathering into a mass, collecting, or heaping up) and *integrating* the accumulated parts into a whole. Cumulative Risk Assessment, then, would examine the *accumulation* (over time, across sources, across routes, etc.) of stressors that can cause adverse effects, and then *integrate* the effects these stressors cause into a picture of the risk caused to the whole (individual or population) by the stressors

[1] In this section, a few basic definitions related to cumulative risk assessment will be discussed. For a glossary of terms, the reader is directed to Section 5.

acting together. Some examples of types of cumulative risk assessments are listed below. Each of these presupposes a defined individual or population[2]:

1. Risks can be added or *accumulated* over time for a single agent or stressor across sources, environmental pathways, or exposure routes. [This is consistent with "aggregate risk" in the FQPA terminology in the box below.] A cumulative risk assessment of this type *integrates* effects by considering differences and interactions related to routes, sources, and time patterns of exposure. This is contrasted to a single chemical assessment which merely adds up exposures across sources, routes, and time as if they all were equal, without regard to how or when they occur, or how these differences affect the final risk result.

2. Risks can be *accumulated* over time (and pathways, sources, routes, etc.) for a number of agents or stressors causing similar types of effects, e.g., a number of carcinogenic chemicals or a number of threats to habitat loss. Again, a cumulative risk assessment for multiple stressors will take into consideration the interactions among stressors, and attempt to address the risks from the combined or *integrated* insult, not merely list risks from individual stressors separately in a table.

3. Risks can be *accumulated* across different types of stressors causing different types of effects, for example chemical, biological, radiological, and physical stressors, causing human health, ecological health, and "quality of life" effects. This is considerably more complex methodologically and computationally than the types of cumulative risk assessments in examples 1 and 2, above. A cumulative risk assessment with multiple types of stressors will address how these stressors can be *integrated* into the overall

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 exposure assessment: An analysis, characterization, and possibly quantification of 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 Food Quality Protection Act also discusses "cumulative effects" from different pesticides which act by the same mechanism of action (or as interpreted, mode of action).

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[2] Populations can be defined by geophysical boundaries, such as a watershed, 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 "in" the population or "out."

estimate of risk for the individual or population. For example, if one were doing a cumulative risk assessment focusing on a wide variety of stressors to a certain (human) community's health, one might also look at how changes in ecological health or quality-of-life in the area affect human health risk.

As a note on #3, individual and community health status and the corresponding health statistics are reflective of *all* stressors in the lives of the population, across all types of effects. When attempting to compare health statistics from a certain area with the results of a narrower cumulative risk assessment, this should be kept in mind. Combining different types of risks will also require more than just an analytical process; it also requires a deliberative process. This will be discussed more fully in Chapter 4.

We have used the key concepts of *accumulation* and *integration* to craft the following definition:

> **cumulative risk assessment**: The examination of the *accumulation* (over time, across sources, across routes, etc.) of stressors or exposures that can cause adverse effects, and then the *integration* of the effects these stressors or exposures cause into an estimate and characterization of the risk caused to the individual or population by the stressors *acting together*.

NEPA's "Cumulative Impact" Definition

CEQ 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

We believe that this is a broad definition, but not so broad that any risk assessment will fit. These definitions clearly exclude assessments which examine a single pathway for a single chemical (no accumulation over various sources, routes, time, different stressors), or even assessments which look at a number of stressors but merely list stressor risks separately (no integration of how they act together to affect overall risk).

We also believe that the definition used here is consistent with the sense of most definitions of "cumulative" such as are included in NEPA, FQPA, or defined by other groups such as the EPA Science Policy Council's Cumulative Risk Subcommittee[3].

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

Cumulative risk assessment is conceptually an analytic-deliberative process (NRC, 1996). It includes both analytic (i.e., rigorous, replicable methods, evaluated under the agreed protocols of an expert community) and deliberative (i.e., stakeholder-value-and-judgment based) parts. Much of what is discussed in Chapter 2, the Planning 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. These include 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 Interpretation Phase, especially where risks of different types are being evaluated and combined.

Cumulative risk assessment, because of this analytic-deliberative process, can be applied to a variety of different problems where analysis of the overall impacts of multiple sources, stressors, chemicals, 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 all 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.

The Core Principles of Community-Based Environmental Protection (CBEP)

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, 1999b

Cumulative risk assessment can also be used in a community-based assessment approach, such as is outlined in EPA's *Framework for Community-Based Environmental Protection* (USEPA, 1999b). The CBEP approach (see box above) encompasses both ecological and human health assessments, and Cumulative risk assessment, being a population-based or place-based analytic-deliberative process, is ideal for CBEP-type applications.

Cumulative risk assessment is also applied in ecological assessments. The definition of

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[3] The Council Cumulative Risk Subcommittee has developed the following working definitions for cumulative risk, which incorporate both the accumulative and integrative aspects of cumulative risk assessment: *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.

cumulative ecological risk assessment, as given in the EPA's 1998 *Guidelines for 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 recent Society of Environmental Toxicology and Chemistry publication (Foran and Ferenc, 1999) discusses multiple stressors in ecological risk assessment, and gives a good overview of the topic of cumulative ecological risk assessment.

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

Although it is possible to use cumulative risk assessment for research, that is, to form hypotheses and test them by analyzing data, it is far more likely that cumulative risk assessment will be used as a tool in decision making.

Decisions can be at a wide variety of levels, from a neighborhood group evaluating ways to improve or safeguard their 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 Framework, such decisions usually involve more than the basic science and analysis that make up the "scientific" part of risk assessment. Robert T. Clemen, in his book *Making Hard Decisions* 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. (Clemen, 1996, page 5)

Regardless of the type of decision being made or the decision-making approach, a cumulative risk assessment's analytic part 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. The U.S. EPA's Science Advisory Board (SAB) in their August, 2000, publication *Toward Integrated Environmental Decision-Making* (USEPA, 2000a), constructed a framework for what they termed Integrated Environmental Decision-making (IED). They noted that "The IED Framework recognizes that risks often are experienced simultaneously and are cumulative...". They speak of risk assessments in a very broad way, including human health effects, ecological effects, and quality-of-life effects. The first two phases of the IED, "Problem Formulation" and "Analysis and Decision-making" essentially correspond to the three phases we discuss in this *Framework for Cumulative Risk Assessment*. The SAB's third phase, "Implementation and Performance Evaluation," is beyond the scope of this framework.

The SAB's report (USEPA, 2000a) 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. These will be discussed in Chapters 2-4, as these phases of the cumulative risk assessment process are examined.

The 1996 book *Understanding Risk* (NRC, 1996) also provided much information on the analytic-deliberative aspects of a risk assessment, and devoted 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 on the following page summarizes some of the points made in *Understanding Risk.*

1.6. Organization of this report

This report is organized to follow the general process steps for a cumulative risk assessment, namely a planning and problem formulation phase (Chapter 2), an analysis phase (Chapter 3), and a synthesis and interpretation phase, where the Risk Characterization is completed (Chapter 4). Chapter 5 is a glossary of terms, followed by References in Chapter 6. For certain topics throughout this Framework, a more in-depth discussion was warranted than the main text would conveniently allow; these have been placed in several Appendices.

Some Thoughts on Risk Characterization

The NRC book *Understanding Risk* (NRC, 1996) has risk characterization as its primary focus. In their conclusions, NRC states:

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, data bases 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: diagnose the kinds of risk and the state of knowledge, describe the legal mandate, describe the purpose of the risk decision, describe the affected parties and anticipate public reactions, estimate resource needs and timetable, plan for organizational needs, develop a preliminary process design, and summarize and discuss the diagnosis with the responsible organization.

The above quotes are from NRC, 1996, pages 2-8. Emphasis is in the original.

2. THE PLANNING 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" in the *Framework for Ecological Risk Assessment* (USEPA, 1992b), the NRC book *Understanding Risk* (NRC, 1996), *Toward Integrated Environmental Decision-Making* (USEPA, 2000a) and elsewhere (e.g., USEPA, 1997a). It is a phase where, according to NRC, "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) . Planning and Scoping of the assessment are often thought of as being part of the Problem Formulation phase, although the 1997 *Planning and Scoping* guidance treats Planning and Scoping as a separate activity before problem formulation begins (USEPA, 1997a). Whether it is considered a separate phase or not, it takes place at the very start of the process of doing a cumulative risk assessment. For convenience, this section incorporates both Planning and Scoping and Problem Formulation into the Planning and Problem Formulation Phase.

2.1. Planning and Scoping

Risk assessments are done within some context, that is, they are usually done 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. They may be public officials, risk experts, community leaders, or any number of other "interested parties." Planning and scoping begins with a dialogue among these interested parties.

Among these interested parties, there 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 will call this person or group the "risk manager," and for ease of discussion, will discuss the risk manager as if it were a single person.

Also among the interested parties is a person or group of persons expert at doing the scientific part of risk assessment. Sometimes called the "risk experts," we have chosen here to call this person or group the "risk assessor." The risk assessor is usually responsible for getting the risk assessment done, by analyzing the probability of adverse effects from stressors. In fact, due to the complex nature of cumulative risk assessments, the "risk assessor" in most cumulative risk assessments will involve a multi-disciplinary team of scientists, engineers, economists, computer experts, statisticians, and other experts.

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. The risk manager, risk assessor, and interested and affected parties, if any, make up the "risk assessment planning team." In the initial phase, "risk assessors, risk managers, and interested and affected parties seek agreement through extensive dialogue and discussion on what analytical and deliberative steps need to be taken by whom, by when, and why -- if not how." (USEPA, 2000a)

In the SAB's report *Toward Integrated Environmental Decision-Making*, they explain 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 of the following sections are important, and should be documented by the team for several reasons. Written records can be referred to by assessors and people at public meetings. They can also help prepare for response to comments, and begin establishing a peer-review record for any later decisions or plans that need to be peer reviewed (USEPA, 2000b).

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 risk manager must explain why the assessment is being performed, and what questions need to be answered. 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, since differing sense of purpose among the team will lead to problems later.

The list of questions to be addressed (and hopefully answered) may influence the management goals (see box at right), risk management options, key participants, data sources, selection of assessment endpoints, approach, and the schedule for developing the assessment.

The manager and assessment planning team must discuss any regulatory or legal basis for the risk assessment, and what kind of information is needed to satisfy such requirements.

The previous discussion follows the typical situation where the risk manager is presented as an independent decision-maker, 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, such as a local citizens' board. For example, the risk assessment may indicate that mitigation of risks may not be significantly affected by any permit decisions but will depend instead on local zoning decisions or on decisions which affect traffic patterns in a community. This is one of the reasons why in the final step in the planning and problem formulation phase, the discussion of possible outcomes (discussed in section 2.3), is so important.

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

2.1.2. Defining the Scope of Analysis and Products Needed

Scoping a cumulative risk assessment effort defines the elements that will or will not be included in the risk assessment[4] (USEPA, 1997a). These include the stressors, sources, pathways, routes, and populations to be evaluated. Initially, the risk assessment planning team needs to 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. Limitations in scope can be geographical (such as political or ecological boundaries), environmental (such as assessing only certain media), demographic (such as assessing only risks to children or asthmatics), statutory, or by using other criteria such as data limitations. The issue of "background" exposures should be discussed and agreements reached (see Appendix E). An adequate assessment scope should make it clear what's included and what's excluded from the assessment. Care must be taken to reconcile the limitations of scope with the list of questions to be answered in the statement of purpose. If, for example, data limitations preclude the addressing of certain of the questions outlined in the purpose, the list of questions to be addressed must be modified and the risk assessment planning team agree to the narrower scope of the assessment.

Reasons for choosing the particular scope of the assessment, and how it will address the questions posed in the purpose statement, must be stated explicitly. Defining the scope of the assessment should include details on limitations on 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 methods available. In cases where an element of risk is likely to be important, but no valid data are available, the assessor must 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 through brainstorming with all participants, the participants should discuss the need and availability of technical information and how such information may affect the overall uncertainty of the assessment. Using input from the risk assessor, the risk assessment planning team must determine what elements will and will not (or, can and cannot) be included in the risk assessment. 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.

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

As examples of some of these scoping elements, 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 human activities (e.g., smoking, other so-called "lifestyle activities") or natural phenomena. Stressors that are not physical, chemical, or biological, such as economic or other quality-of-life stressors may also be identified.

Possible population elements to be assessed usually focus on the entities that are at risk, e.g., populations, communities, ecosystem functions, or vulnerable subpopulations such as persons with certain diseases, or persons at vulnerable life stages, such as children. The more specifically defined these can be, the more focused the analysis can be. This will be helpful in interpreting results of the assessment.

2.1.3. Agreeing on participants, roles and responsibilities

The risk assessment planning team will usually recommend others who should participate in the assessment's 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. Assessments will usually require substantial technical expertise in the analytic portions of the assessment. Some of the fields of science that may be needed or helpful include toxicology, epidemiology, ecology, risk assessment, exposure assessment, fate and transport modeling of various sorts (e.g., indoor and outdoor air, surface and drinking water), computer science (including geographical information systems [GIS]), chemistry, biology, various engineering fields (e.g., chemical, mechanical, industrial, civil), economics, sociology, and others.

For the deliberative portions of the assessment, there can be a number of stakeholders and other interested parties that should be considered for participation. The box at the right lists some examples to choose from among interested or affected parties for the deliberative portions of the assessment.

Examples of Possible Interested or Affected Parties (Stakeholders) (adapted from USEPA 1999b)

State governments	Civic organizations
Tribal governments	Business owners
Local governments	Trade associations
Community groups	Labor unions
Grassroots organizations	Public health groups
Environmental groups	Academic institutions
Consumer rights groups	Cooperative ext. progs.
Religious groups	Impacted citizens
Civil rights groups	Other federal agencies

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 [hereafter, the "Commission"] (1997) suggests the following questions to identify potential interested or affected parties (stakeholders):

- 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?

It has become increasingly recognized as important that stakeholders be involved in risk assessment (e.g., NRC 1996, Presidential/Congressional Commission... 1997, USEPA 1996a, 1997a, 1998a, 1999b, 1999c, 2000a). The Commission suggested guidelines for stakeholder involvement (see box at right).

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 at right, 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,

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, don't 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. Don't 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 stakeholder 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 if any, such incentives can be provided, based on the scope, level of effort, and financial constraints of the risk assessment project.

Roles and responsibilities for technical and non-technical participants (i.e., ground rules for participants) should also be proposed by the planning team, depending upon the schedule, approach, and level of effort that is envisioned for the risk assessment. There will be several key points in the risk assessment process where stakeholder input will be critical. Some of these are the agreements on purpose, scope, and approach. Each project should define and agree upon a list of critical points for stakeholder input.

In spite of increased emphasis on stakeholder participation, however, there are instances where it may not be appropriate for large scale stakeholder involvement. EPA (as the decision maker) must determine whether stakeholder involvement in a cumulative risk decision will be useful and what objectives it may accomplish to plan the public involvement process. 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 (EPA, 1998). Sometimes citizens choose not to participate because they feel it will not influence the outcome, the issue is too complex or technical, the effort is too great, or because the decision process is unclear (EPA, 2001b).

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 simple methods which rely heavily on conservative simple 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 include what level of uncertainty in the risk estimates is acceptable to the participants, the intended use and audience, time and money resources available, and the amount, quality and accessibility of data. In making the decision on approach, there will need to be an understanding of both the level of effort necessary for conducting an assessment of the sort selected, with an insight to alternatives, and the features and limitations of the selected approach, in comparison to other approaches.

2.1.5. Agreement on the Resources Available and Schedule

Schedule and resources are often interrelated. They may also affect whether the work is performed in-house by the organization or team desiring the assessment, or by contractor or other external source. The need to meet external deadlines or coordinate with schedules of other organizations may become an overriding factor in defining what will be prepared. Assessments requiring short-term, low budget efforts, or preliminary screening assessments, may not have the scope, time or resources where extensive stakeholder involvement is necessary or beneficial. For assessments, especially those where there is extensive stakeholder involvement, a budget and time schedule should be developed and known by all participants.

2.2. Problem Formulation, Conceptual Model, and Analysis Plan

Problem formulation is an initial part of the cumulative risk assessment. The outcome of the problem formulation is a conceptual model that describes how a given stressor might affect health or ecological components of the assessment. The conceptual model serves as a basis for the analysis plan, which is used to focus the analysis phase of the assessment. These three components are discussed in the sections below.

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 describes the relationship between the stressors, the population exposed, and the assessment endpoint that will be addressed in the risk assessment.

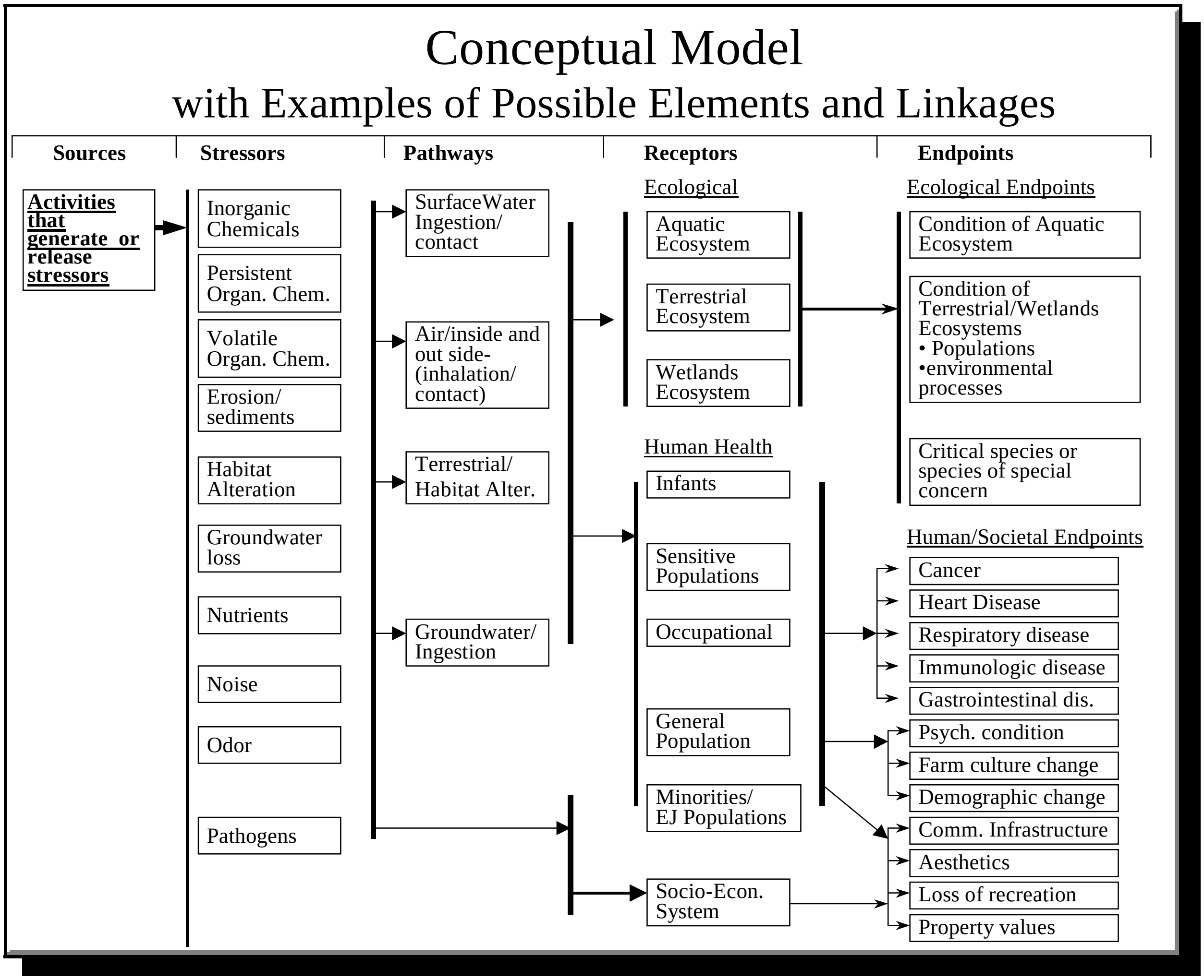

Figure 3. Generic conceptual model (from USEPA, 2001c).

2.2.2. Developing the Conceptual Model

A conceptual model is both a written description and a visual representation of actual or predicted relationships between humans (or populations, 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 needs to distinguish between what is known or determined and what is assumed. Also, it needs to include a discussion of uncertainties in the formulation of the assessment. In some cases, conceptual models will be submitted for peer review. A general conceptual model is provided in Figure 3 (previous page).

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

The Science Advisory Board in their report *Toward Integrated Environmental Decision-Making* (USEPA, 2000a) suggests a list of desired outputs from Problem Formulation. These should not only be left to the visual presentation of the Conceptual Model Diagram, but should also be explained in narrative form. They are listed in the box below.

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 of the problem
- Relevant data and models, and possible approaches 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
- The types of factors that will be considered when reaching a decision

From *Toward Integrated Environmental Decision-Making* (USEPA, 2000a)

2.2.3. Constructing the Analysis Plan

The analysis plan is in the final stages of planning and scoping before the risk assessment analysis phase is performed. The analysis plan includes pathways and relationships identified during planning and scoping that will be pursued during the risk analysis phase. Those hypotheses considered more likely to contribute to risk are given priority. The rationale for selecting and omitting risk hypotheses should be incorporated into the plan and included discussion of data gaps and uncertainties. It also may include a comparison between the level of confidence needed for the management decision with that expected from alternative analyses in order to determine data needs and evaluate which analytical approach is best. When new data are needed, the feasibility of obtaining them can be taken into account.

In situations where data are few and new data cannot be collected, it may be possible to extrapolate from existing data. Extrapolation allows the use of data collected from other locations or organisms where similar problems exist. When extrapolating from data, it is important to identify the source of the data, justify the extrapolation method, and discuss recognized uncertainties.

A phased, or tiered, risk assessment approach can facilitate management decisions in cases involving minimal data sets. However, where few data are available, recommendations for new data collection should be part of the analysis plan. When new data are needed and cannot be obtained, relationships that cannot be assessed are a source of uncertainty and should be described in the analysis plan and later discussed in risk characterization.

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

It is useful for the entire team to hold some preliminary discussions, before the analytical efforts of the assessment are started, about the various possibilities of the cumulative risk assessment results and their implications. What conclusions will be associated with various results or risk levels? For example, for a risk assessment team with members from the community, industry, and the 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 possible responsibility to do something about that risk?

Discussions like these will help determine if 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 of the analysis, then it is important to reopen the entire planning and scoping discussion before anything is done in the analysis phase, since the planning and scoping phase has not been satisfactorily completed.

3. THE ANALYSIS PHASE

The risk assessment paradigm most widely used during the past two decades was first documented by the National Research Council (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 done on single chemicals. Nevertheless, it is a useful place to start when considering cumulative risks. There are a number of ways to approach cumulative risk, either starting with the NRC paradigm or using a different approach. Each may present its own challenges in methods, data, and analysis. Four examples of general approaches are described below. There will undoubtedly be others developed as the science advances.

3.1. General Approaches to Cumulative Risk Assessment

There are at least four different general approaches to cumulative risk assessment. These are briefly outlined here. Each of the approaches has advantages and disadvantages, and will likely come up with independently-derived estimates of cumulative risk (i.e., each uses different data upon which to base the estimate). Given the different strengths and weaknesses, it may be useful to use several of these approaches concurrently to strengthen the analysis.

The remainder of Chapter 3 summarizes some of the issues, and the current state of knowledge, for various aspects of these approaches.

3.1.1. Combining Individual Stressor Risks.

For assessors familiar with the 1983 NRC risk paradigm (NRC, 1983), the most conceptually straightforward approach would be to evaluate stressors individually, then combine the individual risks. This can be done either by (a) combining toxicities before calculating risk, an approach sometimes referred to as "combination toxicology" (Carpy, et al., 2000), or by (b) calculating risks for individual stressors and then combining them.

Combination toxicology develops an estimate of combined toxicity for a multi-component stressors such as a mixture, then treats the mixture, for risk estimation purposes, as if it were a single entity toxicologically. Under this approach, chemical mixtures can be evaluated for toxicity addition, independence, synergy, or antagonism, and a risk evaluation done on the mixture using the 1983 NRC risk assessment paradigm. Mixtures of chemicals acting by the same mode of action are sometimes shown to be additive, which will allow several stressors to be "lumped," simplifying the number of different types of stressors which need to be evaluated.

Calculating individual stressor risks and then combining them presents largely the same challenges as combination toxicology, namely, taking interactions into account. Toxicity addition, independence, synergy, or antagonism still need to be evaluated, but since risk estimates for various stressors are often presented as values on the same numeric scale (e.g., as probabilities or as fractions of an RfD or RfC), cancer risks are often just added together, as are non-cancer risks as part of a Hazard Index. Addition of cancer risk estimates or hazard indices without consideration for how these stressors may interact is making an (implicit or explicit) assumption of dose additivity, which requires explanation in an assessment. This will be discussed further in Chapter 4.

Given the current state-of-the-science, combining individual stressor risk, especially by calculating individual risks and combining them, is probably the best known approach to cumulative risk assessment, although there are currently many data gaps (especially in the area of toxicity of mixtures) (USEPA, 2001a). One major drawback is that as the number of stressors increases, the difficulty of determining how the toxicities of all components interact increases exponentially, and it becomes difficult to perform the assessment without many simplifying assumptions. Depending on the tools or robustness of the data set available, the results of this approach may be presented either in the form of probabilities of getting certain adverse effects (e.g., cancer), or, in the case of evaluating exposures relative to a reference level (such as used with the hazard index approach), it may provide a gauge of the potential for effects[5].

3.1.2. Use of Risk Factors Developed from Epidemiologic Associations.

The medical profession has long used "risk factors" 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 (TIAs), 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 factors can be correlated with stroke incidence, and then the risk of stroke from various combinations of these factors can be explored. Physicians use models containing effect-specific risk factors to advise patients of the probabilities of future effects (e.g., stroke, breast cancer) based on 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 remaining in terms of the role played by exposures to many chemicals in the environment in the development of human disease. This approach may be built on links between stressors and effects for more well-studied stressors, but may be limited in both capability for quantification, and coverage for stressors with less robust health effects data bases.

3.1.3. Biomarkers and Biomonitoring.

This approach uses biological measurements – biomarkers – to determine prior exposures

[5] At exposures increasingly greater than reference levels, the potential for adverse health effects increases.

(biomarkers of exposure) or the current health status of individuals (biomarkers of effect). Use of biomarkers for a group of chemicals or stressors which 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 represent exposure to a suite of chemicals. Although this reduces the analytical burden and simplifies the process of estimating cumulative risk, the approach 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). This may be the approach of choice in the future, but the state-of-the-science is not developed enough to make this practicable today in an assessment with large numbers of diverse stressors (although it may be possible to do this for more simple cases). One of the benefits of this method, the development of data which 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. This can be not only costly, but difficult to obtain. This approach uses primarily measurement methods, and also can develop statements of probability of adverse effects of additional incremental exposures. This approavch holds great promise for simplification of a cumulative risk assessment, but few methods exist at this time for applying this approach in a cumulative assessment.

3.1.4. Other Types of Probability Statements.

Not all statements of probability of harm are expressed as probabilities of specific health effects. Bernard Cohen, in his *Catalog of Risks Extended and Updated* (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, construction workers a 227 day LLE, etc., 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. Other bases for risk statements include the quality-adjusted life year (QALY), which has been used extensively in the medical field for cost-benefit analysis and also has been proposed for use in comparative risk analysis (USEPA, 1998f). In a sense, this approach is similar to the second approach, where risks are added, but it differs qualitatively in the types of risk statements derived. These “other” types of probability statements could conceivably be used in cumulative risk assessment.

3.2. Issues Related to the Approach of Combining Individual Stressor Risks

The approach of combining toxicities or individual stressor risks to come up with an estimate of cumulative risk is most similar to traditional health risk assessment for chemicals, and provides a quantitative analysis, yet may include a large degree of uncertainty.

In evaluating the combined effects from different chemicals, there is often an assumption made that chemicals which have the same mechanism or mode of action, and result in the same effects, are additive at any level of exposure or dose (e.g., see ILSI, 1999, page 23). The EPA's Office of Pesticide Programs has prepared guidance on cumulative risk assessments for chemicals with the same mode of action, as required under the *Food Quality Protection Act* (USEPA, 2000i). In this guidance, risks are only added for chemicals having the same mode of action. In some screening-level assessments, risks from individual stressors may be added without consideration of any similarity in mode of action (USEPA, 1998j). The issue of how individual stressor risks contribute to the cumulative risk is critical to this approach, and will be discussed further in Chapter 4.

Among the steps in this approach, the method usually requires (1) some evaluation of what may be important to the cumulative risk of the population, through risk screening or other means, (2) working through an analysis of the individual risks of individual stressors or mixtures, and (3) determining or estimating the way these individual stressors act in combination with one another. The following sections provide a discussion of some of the issues which may be encountered within these steps.

3.2.1. Characterization of Hazard Identification and Dose-Response.

An initial step in the effects assessment component of human health risk assessment is identification of the potential adverse health effects causally linked to the stressors of concern. This is the hazard identification. Factors such as the route of exposure, the type and quality of the effects, the biological plausibility of findings, the consistency of findings across studies, and the potential for bioaccumulation all contribute to the strength of the hazard identification statement.

Dose-response assessment is the characterization of the relationship between the concentration, exposure, or dose of a pollutant or pollutant group and the resultant health or environmental effects. The nature of quantitative dose-response assessment varies among pollutants. Sufficient data exist for a few pollutants, such as the air pollutants ozone or carbon monoxide, so that relatively complete dose-response relationships can be characterized. In such cases, there is no need for extrapolation to lower doses because adequate health effects data are available for humans at environmental levels. Such is not the case, however, for most pollutants. Most epidemiologic and toxicologic data on toxic pollutants typically result from exposure levels that are high relative to environmental levels. Consequently, dose-response assessment methods for most toxic pollutants generally consist of two parts. First is the evaluation of data in the observable range, and second is the extrapolation from the observable range to low doses/risks. Recent terminology refers to the result of analysis in the observable range as the "point of departure," from which extrapolation begins. The approaches used for evaluation in the observable range are similar for all types of effects, while the Agency's current extrapolation methods differ considerably for cancer and non-cancer effects. Efforts are underway to harmonize these two methods.

Important to characterizing hazard and the dose-response relationship is consideration of the processes of distribution, elimination, and metabolism. Specific characteristics of different chemical and biological stressors dictate how they are distributed within the body, how they are eliminated and via what processes, and how they may be metabolized. These may differ with route or circumstances of exposure, as well as characteristics of the exposed population (e.g., life stage, genetic disposition, etc). To the extent that hazard and dose-response characterization is drawn from laboratory animal data, differences or similarities between animals and humans in distribution, elimination and metabolism are critical to the presumption of relevance to humans.

The Agency has clearly defined methods for hazard identification and dose-response assessment for human health. Those described here are largely relevant to the majority of pollutants for which human effect data at environmental exposures are scarce. In multi pollutant risk assessments, however, it is important to consider the role of other pollutants for which exposures eliciting human effects are not uncommon (e.g., ozone, particulate matter and carbon monoxide in ambient air, nitrates or lead in drinking water). As the Agency's methods for cancer and noncancer assessment currently differ, they are summarized separately here.

3.2.1.1. Current Methods for Assessing Noncancer Effects.

Due to the wide variety of endpoints, hazard identification procedures for noncancer effects are less formally described in EPA guidance than are procedures for the identification of carcinogens. The EPA has published guidelines for assessing several specific types of noncancer effects, including mutagenicity (USEPA, 1986c), developmental toxicity (USEPA, 1991b), neurotoxicity (USEPA, 1998e), and reproductive toxicity (USEPA, 1996b).

For identification of long-term (chronic) hazards other than cancer, EPA reviews the health effects literature and characterizes its strengths and weaknesses, using a narrative approach rather than a formal classification scheme. Available data on different endpoints are arrayed and discussed, and the effects (and their attendant dose/exposure levels) are described. Particular attention is given to effects that occur at relatively low doses or that may have particular relevance to human populations. Information is presented in a narrative description that discusses factors such as the methodological strengths and weaknesses of individual studies (as well as the overall database), the length of time over which the studies were conducted, routes of exposure, and possible biological mechanisms. EPA considers the severity of effects, which may range from severe, frank, effects that can cause incapacitation or death, to subtle effects that may occur at the cellular level but are early indicators of toxic effects. Not all effects observed in laboratory studies are judged to be adverse. The distinction between adverse and non-adverse effects is not always clear, and considerable professional judgment is required in applying criteria to identify adverse effects. All of these observations are integrated into a presentation that gives a concise profile of the toxicological properties of the pollutant.

The inhalation reference concentration (RfC) and oral reference dose (RfD), established by Agency consensus after external peer review, are the primary quantitative toxicity values for use in noncancer risk assessment. The RfC and RfD are defined as estimates, with uncertainty spanning perhaps an order of magnitude, of an inhalation exposure or oral dose, respectively, to the human population (including sensitive subgroups) that are likely to be without appreciable risks of deleterious effects during a lifetime. The RfC or RfD is derived after a thorough review of the health effects data base for an individual chemical and identification of the most sensitive and relevant endpoint and the principal study(ies) demonstrating that endpoint. The methodology for the RfD derivation is discussed in Barnes and Dourson (1988); inhalation RfCs are derived according to the Agency's *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (USEPA, 1994). The RfC or RfD should represent a synthesis of the entire data array. The evaluation of and choice of data on which to base the RfC or RfD derivation are critical aspects of the assessment and require scientific judgment. The Agency, under the auspices of a Technical Panel under the Risk Assessment Forum, is currently evaluating the RfC and RfD methodology as to the need for revisions and improvements.

Derivation of the RfC or RfD begins with identification of the critical adverse effect from the available valid human and animal study data, followed by identification of a lowest-observed-adverse-effect level (LOAEL) or, preferably, a no-observed-adverse-effect level (NOAEL). The LOAELs or NOAELs from animal studies are converted to human equivalent concentrations (HECs) using dosimetric methods (described in USEPA, 1994). The NOAEL [HEC] or LOAEL [HEC] from one or a few studies that is representative of the threshold region of observable effects is the key value gleaned from evaluation of the dose-response data.

The RfC or RfD is then derived by consistent application of uncertainty factors (UFs), generally a 1, 3 or 10, to account for recognized uncertainties in the extrapolation from the experimental data and exposure conditions to an estimate (the RfC or RfD) appropriate to the assumed human lifetime exposure scenario (Barnes and Dourson, 1988; USEPA, 1994). The standard UFs are applied as appropriate for the following extrapolations or areas of uncertainty: 1) Laboratory animal data to humans; 2) Average healthy humans to sensitive humans; 3) Subchronic to chronic exposure duration; 4) LOAEL to NOAEL; and 5) Incomplete data base.

The composite UF will depend on the number of extrapolations required. RfCs have been derived using composite UFs that range from 10 to 3,000, with most RfCs using factors of 100 to 1,000. The use of order-of-magnitude uncertainty factors for RfCs and RfDs and the definition of the RfC or RfD as having "uncertainty spanning perhaps an order of magnitude" are indications of the general lack of precision in the estimates.

In addition to toxicity related to chronic exposures, many hazardous air pollutants (HAPs) also can cause toxic effects after acute (short-term) exposures lasting from minutes to several hours. Indeed, for some pollutants acute exposures are of greater concern than chronic exposures. The hazard identification step for acute effects is comparable to that for chronic effects, with the primary difference being the duration of exposure. Methods for dose-response assessment of acute exposures are substantially similar to the approach for chronic exposure. Risk assessment for acute inhalation exposure is complicated by the steep concentration-response curves that are often observed, and because small differences in exposure duration (in some cases, a few minutes) need to be taken into account. Because increased exposure duration increases the incidence and severity of response, acute toxicity criteria or exposure guideline values are developed for a specified duration (e.g., one hour). While several EPA offices have addressed acute exposures across a variety of regulatory programs, we have only recently drafted Agency-wide guidance on how to assess toxic effects from short-term inhalation exposures. This guidance for acute reference exposure (ARE) levels, when completed, will assist Agency acute risk assessment activities for inhalation exposures (USEPA, 1998d).

3.2.1.2. Current Methods for Assessing Cancer Risks.

The EPA's 1986 *Guidelines for Carcinogen Risk Assessment* (USEPA, 1986d) provide guidance on hazard identification for carcinogens. The approach recognizes three broad categories of data: (1) human data (primarily epidemiological); (2) results of long-term experimental animal bioassays; and (3) supporting data, including a variety of short-term tests for genotoxicity and other relevant properties, pharmacokinetic and metabolic studies, physical/chemical properties, and structure-activity relationships (SARs). In hazard identification of carcinogens under the 1986 guidelines, the human data, animal data, and "other" evidence are combined to characterize the weight of evidence regarding the agent's potential as a human carcinogen into one of several hierarchic categories or groups: A) Carcinogenic to Humans; B) Probably Carcinogenic to Humans; C) Possibly Carcinogenic to Humans; D) Not Classifiable as to Human Carcinogenicity; and E) Evidence of Noncarcinogenicity for Humans.

In 1996, EPA proposed major revisions of the carcinogen hazard identification scheme. The proposed revision to the cancer risk assessment guidelines (USEPA, 1996c), which has undergone subsequent revisions as a result of Scientific Advisory Board reviews (e.g., USEPA, 1999e), focuses on narrative statements describing the main lines of evidence and their interpretation, replacing the current alphabetic designations. The proposed guidelines also replace the system of stepwise consideration of different types of data with a single comprehensive evaluation process that stresses the coherence of various data elements. The result is a single scientific interpretation that evaluates, to the extent possible, how well the commonality of mode of carcinogenic action between human beings and the various test systems has been established. Emphasis is also placed on defining the qualitative conditions under which carcinogenic hazards might be expected. If warranted, limitations to the finding of carcinogenic hazard can be drawn based on route of exposure, existence of other factors needed for tumorigenesis, and doses below which elevation of cancer risk is not expected.

EPA's 1986 *Guidelines for Carcinogen Risk Assessment* adopted a default assumption that chemical carcinogens would exhibit risks at any dose (USEPA, 1986d). This is often called the "no threshold" assumption, that is, unlike non-carcinogens, there is no concentration below which there is no risk. Extrapolation of cancer risk using the linearized multistage model, which results in a linear extrapolation of risk in the low dose region, was proposed as a reasonable upper-bound on risk, and this approach has been used for most chemicals with adequate data since then. The 1986 guidelines did allow that when data supported it, other models could be used in addition to the default linearized model. The *Proposed Guidelines for Carcinogen Risk Assessment* (USEPA, 1996c), however, stressed that when there are adequate mechanistic data to suggest that other models would be more appropriate to estimate low exposure risk, they may be used on a case-by-case basis *in lieu* of the linearized multistage model. In the absence of such data, the assumption of response linearity is maintained, although the modeling scheme has been simplified.

In cancer dose-response assessment, the evaluation of data in the observable range is similar to that for noncancer effects. The method of extrapolation to lower doses from the point of departure, however, differs depending on whether the assessment of the available data on the mode of action of the chemical indicates a linear or nonlinear mode of action. For linear extrapolation, a straight line is drawn from the point of departure to the origin (i.e., to the point where dose and response are both zero on the dose-response curve), and the risk at any concentration is determined by interpolation along that line. A linear mode of action serves as a default when available evidence is not sufficient to support a nonlinear extrapolation procedure, even if there is no evidence for DNA reactivity.

Nonlinear methods (where data support them) or a margin of exposure approach are recommended when there is sufficient evidence to support a nonlinear mode of action. A nonlinear mode of action could involve a dose-response pattern in which the response falls much more quickly than linearly with dose, but still indicating risk at low doses. Alternatively, the mode of action may theoretically have a threshold if, for example, the cancer response is a secondary effect of toxicity or an induced physiological change which is a threshold phenomenon.

3.2.1.3. Time-Related Issues with Dose-Response Curves for Cumulative Assessments.

Cumulative risk encompasses repeated exposures to a single stressor or exposures to multiple stressors (see definition, section 1.3). This has implications with regard to the dose-response assessment method used. Most exposure data used in developing a dose-response relationship (with the exception of some life-stage related effects such as developmental toxicity) is usually treated as "cumulative" for the duration of interest, but may not match the exposure regimes seen in actual assessments. Moreover, in the case of non-cancer effects for many chemicals, there is **no** explicit description of the dose-response relationship for use in the risk assessment, since the objective has usually been development of an RfC or RfD (a level at which effects are considered low probability) to be compared with estimates of continuous exposure or daily doses.

Some Issues Concerning Time Sequence of Exposures in Developing Dose-Response Relationships for Cumulative Risk Assessment

- What types of chemicals are likely to function as "promoters" or to cause damage that will make a person more susceptible to other exposures later? What is known about how they work?
- What are some of the ways time sequencing is dealt with in considering risk from effects which are thought to have a threshold? Can these methods be adapted to cumulative risk assessment?
- What work has been done in looking at non-chemical stressors which can cause a person to be more susceptible to exposure to chemicals later? Is anything known about the permanence or transitory nature of the damage done by these non-chemical stressors?
- What are the specific factors which need to be known to properly evaluate risks from exposures to different stressors at different times? What circumstances, types of stressors, or non-chemical stressors may be important?
- What new types of problems will cumulative risk assessment present to the practitioner confronted with a population exposed to a non-constant mixture of stressors over a period of time?

In the case of linear carcinogens, this cumulative exposure assumption has been carried into the risk assessment step. Regardless of the details of the exposure circumstances for 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 non-linear carcinogens assessed in cumulative risk assessments[6], the details and sequence of exposure may be important, both in developing the dose-response relationship and in predicting risk associated with exposures of interest.

As some chemicals may have the ability to affect an organism's response to other

[6] The draft cancer guidelines (USEPA, 1996c) explicitly recognize the potential for non-linear dose response. It is only in the case where non-linear response is modeled that time sequence of exposure can be considered in the risk assessment.

chemicals, consideration of the time sequence of exposure may take on an additional layer of complexity in multiple chemical cumulative risk assessments.

3.2.1.4. Issues Associated with Assessing Mixtures of Stressors.

While some potential environmental hazards involve significant exposure to only a single compound, most instances of environmental contamination involve concurrent or sequential exposures to a mixture of compounds. These various components may induce similar or dissimilar effects over exposure periods ranging from short-term to lifetime. Within EPA's guidelines on assessing health risks from chemical mixtures, mixtures are defined as any combination of two or more chemical substances regardless of source or of spatial or temporal proximity that can influence the risk of chemical toxicity in the target population (USEPA, 1986b). In some instances, the mixtures are highly complex, consisting of scores of compounds that are generated simultaneously as by-products from a single source or process (e.g., coke oven emissions and diesel exhaust). In other cases, complex mixtures of related compounds are produced as commercial products (e.g., PCBs, gasoline and pesticide formulations) and eventually released into the environment. Another category of mixtures consists of compounds, often unrelated chemically or commercially, that are placed in the same area for disposal or storage, and have the potential for combined exposure to humans.

Multi-pollutant exposure scenarios can be extremely diverse. Moreover, the quality and quantity of pertinent information available for risk assessment varies considerably for different mixtures. Occasionally, the chemical composition of a mixture is well characterized, levels of exposure to the population are known, and detailed toxicologic data on the mixture are available. Most frequently, some components of the mixture are unknown, exposure data are uncertain or vary over time, and toxicologic data on the known components of the mixture are limited

To address concerns over health risks from multi-chemical exposures, EPA issued *Guidelines for Health Risk from Exposure to Chemical Mixtures* in 1986 (USEPA, 1986b). Those 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 Toxicity Equivalence Factors for characterizing health risks of the class of chemicals including the dibenzo-dioxins 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 binary (two-chemical) mixture (USEPA, 1990a). The concept of toxicologic similarity was also discussed, and is expanded upon in the recent *Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (USEPA, 2001a).

The prediction of how specific mixtures of toxicants will interact must be based on an understanding of the mechanisms of such interactions. It generally is recognized that toxicant interactions may occur during any of the processes that take place with a single compound: absorption, distribution, metabolism, excretion, and activity at the receptor site(s). Compounds may interact chemically, yielding a new toxic component capable of causing a change in the biological availability of the existing component. They may also interact by causing different effects at different receptors sites. Because of the uncertainties inherent in predicting the magnitude and nature of toxicant interactions, the assessment of health risk from chemical mixtures must include a thorough discussion of all assumptions. No single approach is recommended in the Agency *Guidelines*. Instead, guidance is given for the use of several approaches depending on the nature and quality of the data. Accordingly, the most recent *Guidance* describes procedures for assessment using data on the mixture of concern, data on a toxicologically similar mixture, as well as data on the mixture component chemicals. The state of science varies dramatically for these three approaches. The "whole mixture" procedures are most advanced for assessing carcinogenic risk, mainly because of the long use of *in vitro* mutagenicity tests to indicate carcinogenic potency. *In vitro* test procedures for noncancer endpoints are still in the pioneering stage. In contrast, the component-based procedures, particularly those that incorporate information on toxicologic interactions, are most advanced for noncarcinogenic toxicity.

Risk assessment on 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 simple collection of a few component chemicals, the uncertainties include the generally poor understanding of the magnitude and nature of toxicologic interactions, especially those interactions involving three or more chemicals. Because of these uncertainties, the assessment of health risk from chemical mixtures must include a thorough discussion of all assumptions and the identification when possible of the major sources of uncertainty.

3.2.1.5. Hazards Other than Chemical Hazards.

In addition to chemical stressors, there are other broad categories of stressors: biological, radiological, physical, and various other types of hazards can also cause adverse effects. The adverse effects of radiation, such as the radiation from radon gas which infiltrates into a home, are well-known. Biological effects, such as bacterial infections and *Cryptosporidium* outbreaks in drinking water, can have very serious adverse effects. Physical hazards include natural hazards, such as earthquakes, hurricanes, and floods, or man-made hazards, such as traffic accidents. Other types of stressors, including socioeconomic factors and lifestyle conditions, can also cause or exacerbate harmful effects.

The context of a risk assessment might lead a risk assessor to consider the adverse effects from exposure to a number of chemical, biological, physical, or other stressors which present different types of hazards. Chemically, when two stressors cause similar effects (for example, both are cholinesterase inhibitors), the interaction could lead to additive, synergistic, antagonistic, or potentiated effects. Stressors causing different effects may interact in ways to potentiate either or both the effects of the individual stressors, or dampen one or both the effects, or even operate independently of one another (USEPA 2001a). These possibilities also exist for the interactions of chemical stressors with non-chemical stressors. Cumulative risk assessment could encompass the interactions of chemical stressors with biological stressors, physical stressors, ecological stressors, radiological stressors, and other stressors such as socioeconomic or lifestyle conditions (e.g., diet, smoking, health care, housing).

One of the important processes in the development of cumulative risk assessment will be the development of methodologies that can be used to compare and combine the risks from very different types of hazards. The risk assessment methodology for single chemical exposure is well developed, but methods for assessing risks from multiple chemicals, or for combining risks from different types of hazards, such as biological and chemical, or biological and physical, are nowhere near as robust and available.

Although the ultimate aim of cumulative risk assessment might include a combined risk across many different types of hazards for a population, realistically, it will take a great deal of research to develop methods to adequately combine risks across different types of hazards. This will be discussed more in Chapter 4.

3.2.1.6. 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 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).

Vulnerability of a population places them at increased risk of adverse effect. 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 which may be highly susceptible to risks from stressors or groups of stressors due to their age, gender, disease history, size or developmental stage". 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). These same concepts may also be discussed as a group in terms of "population vulnerability." The various ways in which a population may be vulnerable are discussed below in four categories.

The first of these is *susceptibility or sensitivity*. Susceptible or sensitive individuals within a population have a different or more pronounced dose-response relationship when confronted with a stressor. Reasons for susceptibility may be related to any number of factors, including life stage (e.g., children or the elderly may be more susceptible), prior exposure (e.g., developing sensitization reactions, or having had exposures which compromise the immune system), genetic polymorphisms (e.g., genetic susceptibilities which occur in a small but significant percentage of the population), or existing disease state (e.g., asthmatics). Confronted with equal concentrations of a chemical for equal durations, for example, a biologically susceptible individual may show effects while the typical individual within the population would not. Although we generally do not have a lot of data available on this topic, susceptibilities or sensitivities may also exist among races or genders.

The second category of vulnerability is *differential exposure.* While it is obvious by examining a dose-response curve that two individuals at different exposure levels may have different likelihood of effects, this also extends to differences in historical exposure, body burden, and background exposure, which are sometimes overlooked in an assessment.

The third category of vulnerability is *differential preparedness* to withstand the insult of the stressor, and the fourth is the *differential ability to recover* from the effects of the stressor. These last two are linked to what kind of coping systems and resources an individual, population, or community has. Preparedness or recovery is often a crucial factor 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 or recover from a stressor. One aspect of differential ability to recover is illustrated by differing survival rates for the same disease (e.g., Lantz, et. al 1998).

Cumulative risk assessments may be uniquely suited to addressing the issues related to vulnerability. In order to do that, however, there needs to be some relationship between the factors discussed above and changes in risk. At the current state of the science, these factors have not been extensively developed beyond correlations between mortality rates and several socioeconomic factors such as income (e.g., Lynch, et al. 1998).

3.2.2. Characterization of Exposure.

Exposure generally refers to contact of an individual or the study population with the stressor of interest. With regard to human exposure, the Agency defines exposure as taking place at the visible external boundary of the person (e.g., skin, and openings into the body such as mouth and nostrils) (USEPA, 1992c). Following exposure, a chemical or biological stressor may be taken up into the body (e.g., inhaled, or ingested) leading to its availability for absorption into the circulatory system, distribution to various sites within the body, elimination from the body and metabolism or transformation. These processes following contact (exposure) are considered in the hazard and dose-response characterization (see section 3.1).

The general approaches to quantitative exposure assessment are discussed in EPA's *Guidelines for Exposure Assessment* (USEPA 1992c), which suggests three:

• **Direct measurement.** Measurement of exposure at the point of contact *while the exposure is taking place*, measuring both the exposure concentration and the time of contact and integrating them;

• **Scenario evaluation.** Estimation of exposure by separately estimating the exposure concentration and the time of contact, then combining this information through modeling; and

• **Dose reconstruction.** Estimating the exposure from reconstructing the dose through internal indicators such as biomarkers, body burden, or excretion levels.

These same three approaches are useful for evaluating exposure in a cumulative risk assessment. The first approach, direct measurement of exposure, requires personal exposure measurements for individuals within a population. The second approach, scenario evaluation (most often employed by the Agency), is usually done using environmental source evaluations, fate and transport models, population demographics, exposure models, and by constructing exposure scenarios. (This approach often is used by constructing a conceptual model which uses monitoring data for calibration.) The third approach, dose reconstruction, employs markers of exposure and dose. The three different approaches use

Components of Exposure Assessment

• **Characterization of the Source** in terms of the pollutants/stressors released into the environment, release rates, or amounts and characteristics of the release.
• **Environmental Fate and Transport Characterization** including how the pollutant/stressor is transported, dispersed and transformed over the area and media of interest.
• **Characterization of the Study Population** in terms of geographic distribution and other characteristics relevant to the exposure pathways or pollutant effects of concern.
• **Exposure Characterization** is the spatial integration of the pollutant concentration/stressor intensity with the study population.

different data for input to the exposure estimate, and for that reason, can be complementary for verifying or validating estimates by either of the other approaches.

For most aspects of exposure assessment, the 1992 *Guidelines for Exposure Assessment* provide a detailed discussion which can be used as the basis for exposure assessments within cumulative risk assessments. Agency documents providing more in-depth discussion of assessment methods for particular exposure routes or pathways (USEPA, 1999g) are also available. There are several aspects of cumulative risk assessments which were not addressed by the *Guidelines*. One of these, the concept of *aggregate exposure* (generally meaning the sum of exposures for a stressor from multiple sources and routes over time), has been considered in the development of some drinking water and air quality standards, and became a major focus of the *Food Quality Protection Act of 1996*[7].

Although the concept of aggregate exposure focuses on a single chemical or stressor, it does so from the standpoint of a defined receptor or population, and theoretically includes all relevant pathways by which a chemical can reach the population. In Figure 2, a single circle marked “chemical” or “stressor,” with the arrow that connects it to the population, represents aggregate exposure.

Across the various EPA programmatic areas, Offices are currently assessing or are moving toward assessment of aggregate exposures, effects of mixtures, and cumulative risks. Several other novel aspects of exposure assessment within the framework of a cumulative risk assessment are discussed in the sections below.

3.2.2.1. The Time Dimension of Exposure.

As discussed in section 3.2.1.3, risk assessment for carcinogens has historically used a linear, non-threshold theory[8] which attaches the same risk of effect to a unit of exposure

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[7] The *Food Quality Protection Act of 1996* used the term “aggregate exposure” eight times. Although it did not define the term, it was used in the context of multiple exposures to a single pesticide chemical residue from a variety of pathways. Typical of the wording is that on page 110 STAT. 1518 of the Act, which directs the Administrator to consider, among other relevant factors, “available information concerning the aggregate exposure levels of consumers (and major identifiable subgroups of consumers) to the pesticide chemical residue and to other related substances, including dietary exposure under the tolerance and all other tolerances in effect for the pesticide chemical residue, and exposure from other non-occupational sources.”

[8] The linear, non-threshold theory is a convention applied when time data are not available. Although time-to-tumor models and the Armitage-Doll model structure have been considered since the 1960s, their evaluation requires data that are not routinely obtained in experiments.

regardless of when the exposure occurs during a lifetime[9]. For this reason, average exposures and doses have been used extensively in risk assessments for cancer. For non-cancer effects, however, a threshold is usually assumed, and effects may be contingent upon exposure at certain "critical periods" in a person's lifetime (e.g., certain critical periods during pregnancy for developmental toxicity, or exposure while a child during development). The initiator-promoter model of carcinogenesis, first described with mouse skin studies almost 60 years ago[10], provides an example of the role that can be played by multiple chemicals and time sequence of exposure in eliciting a physiological effect or disease such as cancer. This has implications for risk assessment. 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.

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 the ILSI *Framework for Cumulative Risk Assessment*: "Data collected specifically to support a cumulative exposure assessment should conserve the covariance and dependency structures associated with the chemicals of concern.... For example, when residue levels of each chemical within a set of chemicals are measured concurrently in an environmental matrix, such as food, the probability of one chemical being absent when another is present is implicit in the analytical results.... The combination of independent data sets to produce a cumulative assessment will require inclusion of estimated covariance factors, and will necessarily reduce the reliability of the analyses." (ILSI, 1999)

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[9] A typical unit of dose used in exposure assessments for carcinogens is the Lifetime Average Daily Dose (LADD) (USEPA, 1992c). By averaging dose over a lifetime, one is assuming that it doesn't make any difference to the ultimate toxicity when the exposure takes place, or what the exposure pattern is. This assumption, a derivative of "Haber's Rule"(Haber, 1924; a relationship developed in a study of mustard gas effects which showed that the effect – over a limited range – was proportional to the product of concentration of the gas times exposure duration), fits well with the linear, non-threshold approach to carcinogen risk assessment. Although the LADD is currently widely used in risk assessment, it will not be accurate if the dose-response curve is not "linear non-threshold."

[10] The model system for mouse skin carcinogenesis (Rouse and Kidd, 1941; Mottram, 1944; Berenblum and Shubik, 1947) involved the alteration (or "initiation") of individual cells as a result of a single dose of a chemical carcinogen. Subsequently, the application of a second agent, which itself was not considered carcinogenic, elicited skin papilloma (indicating "progression").

Some Examples of Exposure Models which Consider Time Aspects

Calendex (Novigen Sciences, Inc), integrates different pathways e.g., dietary (food and water), and residential, and routes (oral, dermal, inhalation) of exposure using a calendar-based probabilistic approach . One of the important factors of this approach is it provides estimates of risk which 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 pre- and post use of a chemical, as well as 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 analysis of exposure. For example, specific, single day exposures which are multipathway (e.g., one could perform an assessment on June 21 if one knew of specific exposure timing with which we were concerned).

APEX - The Air Pollution Exposure (APEX) model is based on the pNEM probabilistic National Ambient Air Quality Standards 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 CO), 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, which represent specific *population cohorts* and are tracked 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; they are 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 the LifeLine Model, developed under a cooperative agreement between EPA/OPP and Hampshire Research Institute (Hampshire Research Institute, 1999, 2000); the Stochastic Human Exposure and Dose Simulation Model (SHEDS), under development by EPA's Office of Research and Development (Zartarian, *et al*., 2000), and the Cumulative and Aggregate Risk Evaluation System (CARES), under development by member companies of the American Crop Protection Association (APCA, 1999).

Cumulative risk assessment presents challenges in matching exposure estimates with dose-response relationships. In a cumulative risk assessment, the time sequence of exposure may be particularly important. As discussed in section 3.1.3, ideally, the dose-response assessment will indicate the importance of the time sequence for the chemical(s) of interest in the assessment. In cumulative assessments involving these chemicals, in the same way, it may become important to characterize the details and sequence of exposure to the exposed population (see box above), so there will be a match in not only the form, but also the assumptions between the dose-response relationship and the exposure or dose estimate.

3.2.2.2. Variation of Mixtures.

Unlike exposure assessments for single chemicals, the cumulative assessment is likely to have to evaluate the exposure to mixtures, whether mixtures of chemicals or mixtures of chemicals and other stressors. Evaluating exposure to mixtures requires characterizing the mixture at the point of contact, but often the data are for the composition of the mixture at the source. In these cases, the assessment may need to include a fate and transport modeling component to predict how that combination of chemicals may have changed both over time and space, as the chemicals move to the point where (human or ecological) receptors are exposed. The chemical mixture at the point of contact with a receptor might be quite different from the original mixture generated at the source, since chemicals move differently through the environment and can have different rates of degradation in the environment (i.e., mixtures such as PCBs are sometimes said to "weather" over time).

EPA has developed information to assist in determining what chemical mixtures people are likely to be exposed to under different situations. While monitoring at the exposure point can be the most accurate way to determine the specific nature of mixtures to which receptors are exposed, there are also numerous modeling tools which can be used to predict the transport, dispersion and transformation of chemicals in the environment. A variety of fate and transport models as well as the parameters needed to run the models (such as vapor pressure, partitioning coefficients, solubility measures, etc.) have been developed and activities continue to improve them. These models can assist the assessor in predicting the nature of the mixture at the point of contact.

The fact that mixtures can change or degrade over time and space makes exposure assessment within the cumulative risk assessment a particular challenge when exposure measurements are not available. Both exposure measurements at the receptor and predictive approaches are applicable, and each pose its own challenges in implementation, including resource requirements and uncertainty.

3.2.2.3. Sources and Pathways of Exposure.

Pathways of exposure within a cumulative risk assessment can be many and varied, as can the sources of chemicals or stressors into the environment. Consider, as sources, for example, consumer products or pesticides used, improper disposal of hazardous waste or hazardous material, discharge of wastewater into surface or ground water, motor vehicle emissions, or emissions from large (factories, power plants) or small (gas stations, dry cleaners, home heating) point sources.

These chemicals can reach the receptor by a variety of pathways. For example, application of an agricultural pesticide can potentially contribute to a farm-worker population's exposure to that pesticide via inhalation of "drift" during and immediately after application, ingestion of food or water to which the pesticide has been transported or directly applied, ingestion of livestock who have been fed produce to which the pesticide has been applied, and dermal absorption from contact with vegetation or clothing after application. An urban population may be exposed to a volatile organic compound such as benzene from inhalation of outdoor air receiving emissions from mobile sources and various large and small stationary sources (e.g., petroleum refineries, bus stations, truck stops and gas stations), inhalation of air while driving or riding in a car or bus, and inhalation of air inside the home, office or other establishment frequented by a tobacco smoker. A population's exposure results from the aggregate of all of the relevant pathways. The Agency considers the former example as part of pesticide registration under the FQPA, and considers many of the latter in exposure assessments conducted in support of the National Ambient Air Quality Standards and, more recently, in priority setting for the air toxics program.

Sources and pathways for non-chemical stressors such as biological, radiological, and other stressors can be even more varied. Many of these sources and pathways, with which chemical risk assessors may be unfamiliar, were not routinely evaluated within the scope of historical single-chemical risk assessments, but they may be of interest in some cumulative risk assessments. Some of these sources are discussed in section 3.2.5. In many of the items below, they are routinely evaluated in certain types of assessments, but not typically addressed in others. For cumulative assessments, it is useful to have a list of sources of information. One such list can be found in Appendix A.

3.2.2.4. Subpopulations with Special Exposures.

Certain subpopulations can be highly exposed to stressors based on geographic proximity to sources of these stressors, coincident direct or indirect occupational exposures, their activity patterns, or a combination of these factors. A cumulative risk assessment may need to include special emphasis on identifying and evaluating these subpopulations.

Subpopulations at risk of high exposure due to geographic proximity could include workers at a facility which is a source of a stressor or residents near such sources. Specific examples might be people living in the plume from a coal burning power plant, those near and using a polluted water body (for example, for fishing or recreation), or along 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 of those occupationally exposed, who may be exposed to occupational chemicals brought into the house by the worker (e.g., on clothes, breath, etc). Thus, workers or family members may be subject to greater exposures than others in the population without 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 wild animals, farmers or others who get a large percentage of their food from a location near a source of pollution and live in areas with high pesticide use, individuals with 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).

Two examples of the combined impact of high geographic exposure and high exposure activity patterns are runners who run along heavily traveled roadways, and those who fish for food in heavily polluted urban rivers.

It is important to recognize that some heavily exposed populations may also be particularly vulnerable. 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 economically disadvantaged without access to medical care. A cumulative risk assessment may need to take into account potential combinations of high exposure and high vulnerability.

3.2.2.5. Exposures to Non-chemical Stressors.

Depending on the scope of the cumulative risk assessment, the analysis may include non-chemical stressors which could cause adverse effects, or interact with chemical stressors to potentiate or otherwise change the dose-response relationship of a chemical in a specific population.

Assessing exposure to non-chemical stressors may be straightforward, such as in the case of radon exposure. Radioactivity can be sampled, measured, and exposures estimated. Estimating other exposures, such as stress induced by living near hazardous waste sites, or stress due to impact on so-called “quality-of-life criteria,” may not be straightforward at all. Partly, this is because their evaluation moves away from a strictly analytical, scientific, process to a more analytic-deliberative process. Exposure to psychological stressors and stressors that can affect quality-of-life criteria are discussed in more detail in section 4.1.2. Appendix A suggests some further reading on methods relevant to determining exposures to other non-chemical stressors.

3.3. Issues Related to the Approach of Using Risk Factors

[To be added]

3.4. Issues Related to the Approach of Biomarkers and Biomonitoring

[To be added]

3.5. Issues Related to Other Approaches

[To be added]

4. THE INTERPRETATION (RISK CHARACTERIZATION) PHASE

4.1 Risk Estimation

Risk estimation in a cumulative risk assessment will involve some combination of risks, either risks from various stressors[11] causing similar effects, or risks from various stressors causing different types of effects. The stressors may be similar or widely different. Combinations of many types of stressors with different endpoints in a single assessment will quickly cause the risk estimation step to become very complex and difficult. Basic calculation techniques for various single-chemical risks are covered in EPA's various Guideline documents (USEPA 1986c, 1986d, 1991b, 1992c, 1994, 1996b, 1996c, 1998b, 1998e). The following sections discuss how risk estimation in cumulative risk assessments may differ substantially from single-stressor assessments.

4.1.1. Methods for Combining Chemical Risks

One approach to assessing health risk from multiple stressors is to combine the individual risks when the effects are similar (this was example #2 in section 1.3). The simplest example, and one with the longest heritage, is the treatment of all cancer as one endpoint and the combination of the single chemical probabilistic risks using the formula for statistical independence. The result is one probability (risk) for cancer from all the chemical exposures. While this approach could equally well be applied to other toxic endpoints, the differences in how the body reacts to non-carcinogenic insults, and the consequent assumption of a toxicological threshold for many non-cancer effects, has led to a weaker quantitative measure for general risk assessment, the Hazard Index. The formula for the composite cancer risk is preferably applied for mixtures of chemicals with different underlying toxic mechanisms. In

[11] In some cases, it will involve a complex single-stressor exposure over a period of time where response to exposure is not constant. This could be the result in changes in disease state, vulnerability, intervening exposure to different stressors, or other factors which make the response profile change over time.

contrast, the Hazard Index is best applied for toxicologically similar chemicals and is specific to each target organ. The underlying principle, called dose addition (or concentration addition), is also used when converting the multiple exposure levels of the mixture components into the toxically equivalent exposure to one so-called index chemical in the mixture. This latter procedure, called the Relative Potency Factor approach (USEPA, 2001a; Hertzberg et al., 1999) can be specific to one target organ, or if the similarity is justified on mechanistic grounds, can be applied to all toxic endpoints for the chemical group being assessed. The mixture risk is determined from the dose-response curve for the index chemical and so will give different risk estimates for each endpoint. The resulting mixture risks, then, are presented separately for each toxic endpoint or each target organ.

Most multichemical exposures involve dissimilar chemicals, such as metals and pesticides, and so are likely to contribute to joint toxicity by other than dose-additive means. In many cases, the component toxicities influence each other (i.e., are not independent) and so must be considered simultaneously. The traditional approach to toxicologic interdependence has been the determination of synergism and antagonism for categories of pairwise interactions (i.e., those involving just two chemicals). The present EPA mixture guidance (USEPA, 2001a) uses such categories in a interaction-based Hazard Index. This modified Hazard Index incorporates the weight of evidence for pairwise interactions into a formula that adjusts each chemical's contribution to toxicity by all the possible toxic interactions with the other chemicals in the mixture. While immediately useful for regulatory decisions, especially for mixtures of only a few chemicals, such approaches are of limited use and questionable accuracy when addressing more complex mixtures. Current research efforts are seeking to identify toxicologic principles of joint action that are applicable to mixtures of many chemicals (Portier, 2001; Yang, 2001; Hertzberg and Teuschler, 2001).

Another method for assessing the combined risk of a mixture is to use data obtained from testing the mixture itself, rather than building up the mixture risk from data for the component chemicals. Testing of whole mixtures is expensive because environmental mixtures do not stay in constant total dose or composition, forcing testing of many variations of the same mixtures. One relatively inexpensive test method, called the comparative potency approach, involves *in vitro* or short-term *in vivo* experiments that are then numerically scaled or extrapolated to public health risk[12] (Albert, et al., 1983; Lewtas, 1985, 1988; Gandolfi, et al., 1995). Whereas dose addition combines risks of toxicologically similar chemicals, comparative potency models the risks for groups of toxicologically similar mixtures, an approach that requires considerable scientific judgment.

[12] This presupposes the availability of an "index chemical", for which both the simple toxicity test data (e.g., skin painting assay, enzyme activity) and the more comprehensive test data (e.g., 2-year cancer bioassay from which a potency estimate has been derived) are available.

4.1.2. Other Impacts or Effects

Just as the effects from chemical stressors discussed in the previous section need to be sorted into similar effects before being combined, the effects from non-chemical stressors also need to be sorted into similar effect groups. There are a wide variety of effects from biological stressors, for example, and these can be grouped into a number of categories by the types of hazard they pose. Biological stressors, like their chemical counterparts, can interact and change the overall risk in non-additive ways[13]. Obviously, there is an additional difference between chemicals and biological stressors when evaluating exposure. Chemicals may degrade or accumulate in the environment or in tissue, but possible growth and transmittal of biological vectors adds another dimension to the challenge of evaluating exposure.

As cumulative risk assessment requires a broad focus shaped by aspects of the specific problem, other impacts besides chemical-based and biological-based effects may need to be considered and evaluated. As an example, current physical and mental health status and past exposure histories may be a cumulative risk stressor. Economic considerations such as economic status, community property values, source of income, level of income, and standard of living may be stressors in that they affect susceptibility and exposure of subpopulations to certain other stressors. Risks resulting from 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 risk management options deemed acceptable. Depending on the scope of the assessment, so-called lifestyle factors such as smoking habits, nutritional habits and others may be important components of overall risk. Finally, there may be some additional (but hopefully, lesser) risks associated with acceptable remedial options, since adverse effects can be associated with construction and implementation of a remedy or risk reduction option.

In trying to assess all of 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. In an ideal situation – one quite remote from today's state of the science, to be sure – one would also know the mechanism or mode of action by which the stressor causes the effect, allowing more refined grouping by mechanism/mode of action.

4.1.2.1. Stress-Induced Risks.

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[13] A person weakened by one disease may be devastated by a second disease infection which, if the person were healthy, would be fought off easily. This is typical of AIDS victims, for example.

The Agency for Toxic Substances and Disease Registry (ATSDR) held an expert panel workshop in 1995 on the subject of psychological responses to hazardous substances (ATSDR, 1995). In this 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, 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. On the other hand, scientists tend to rely on objective data produced by specialized testing that is subject to statistical analysis.... 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, they 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 needs to 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. (ATSDR, 1995, page 30)

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

4.1.2.2. Quality-of-Life Risks.

Another group of stressors and effects whose evaluation may require a different approach from the traditional NRC risk paradigm are the quality-of-life issues. To evaluate the effects from these types of stressors, a more deliberative approach is needed than is used in, say, cancer risk analysis. EPA's *Guidebook to Comparing Risks and Setting Environmental Priorities* (EPA, 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.

Quality-of-Life impacts are determined by analyzing a set of criteria developed for each community, depending on what they value. 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 given below. These criteria were developed by the State of Vermont's Agency of Natural Resources (State of Vermont, 1991):

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, 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 vet born.

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 individual; the loss of Vermont's landscape and the connection between the people and the land.

Vermont's experience in evaluating these criteria was described as a qualitative description of 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 used here as an example. Some cumulative risk assessments may include quality-of-life criteria as measures of effects, in addition to human health effects or ecological effects. How these very different types of risks may be included in a cumulative assessment is discussed in the following section.

4.1.3. Combining Different Types of Risk

An important aspect of the concept of multiple-agent cumulative risk is that it represents the **combined** risks from the multiple agents or stressors acting together. This means that a stressor by stressor listing of risks does not constitute a cumulative assessment unless this listing can be interpreted in a way that provides an integrated characterization of the overall risk. Therefore, an important cumulative risk assessment activity is determining how (if at all possible) to combine disparate measures of risk and present them in an integrated manner. This is not to say that all cumulative risk assessments must use a single, common metric to describe overall risk, but that the combined effects of the stressors acting together should be discussed and characterized.

The assessment of a single stressor often results in the identification and, possibly, the quantifying of a variety of hazards and risks. For example, a single stressor may be associated with adverse human health effects that result from exceeding a threshold exposure during a brief period of time. These "risks" are often represented by using Margins of Exposure (MOEs) as surrogates (i.e., the margin that exists between environmental exposures and the highest dose believed to be without adverse effects) (USEPA, 1996c). This same stressor may also be associated with adverse health effects that result from longer term or lifetime exposures. These exposures may be presented as the percent of a reference dose (%RfD) or other chronic dose believed to be without adverse effects. Finally, if the same stressor is associated with cancer, risks may be presented as a probability of developing cancer.

The goal of a cumulative risk assessment is to portray disparate risks in a manner that will inform the decision-making process. The general approach to multichemical assessment has been to present separate risk estimates for each toxic endpoint of concern. This approach can be expanded to also include non-chemical stressors in a cumulative risk assessment. Even so, one is left with a complex matrix of hazards and risks for various stressors.

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 to 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.

4.1.3.1. Converting Adverse Effects to a Common Metric

As discussed at the beginning of Chapter 3, there are several different theoretical approaches to cumulative risk assessment. Some of these require synthesizing a risk estimate (or risk indication) by "adding up" risks for different parts of the risk picture. Actual mathematical addition, of course, requires a common metric. Finding a common metric for dissimilar risks (cancer vs. non-cancer, human vs. ecological, etc.) is not strictly an analytic process, since some judgments must 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.

As an example of combining different effects into a common metric and the consequent judgment needed to achieve a common metric, the EPA Office of Pollution Prevention and Toxics in 1999 released its CD-ROM called "Risk-Screening Environmental Indicators Model, Version 1.0" (USEPA, 1999h)[14]. In this model, emissions for both carcinogens and non-carcinogens 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 non-carcinogens is based on the RfD. According to the authors, it is possible to relate these two scales by making a judgment as to how they relate. 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).

[14] As of this writing, EPA has RSEI version 2.0 in beta test. Details are at www.epa.gov/oppt/env_ind/beta_test.htm.

Obviously, as Bouwes and Hassur acknowledge, equating an Hazard Quotient value of 1.0 (exposure 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. This particular part of the assessment is deliberative in nature. 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, or converted to a scale based on the judgments and values of the persons doing the assessments (USEPA, 1993b, 1998f, 1999f). When converting such diverse endpoints as human health, ecological, and quality of life, comparative risk is almost always involved, and this makes combining of diverse risks a *deliberative* rather than an analytic process.

There have been some attempts to quantify diverse risks in a common metric without resorting to the values needed as input for comparative risk. It has been suggested that "time is the unit of measure for the burden of disease"; whether the disease results in disability or premature mortality (Murray, 1994). Based 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 and the years of life lost due to premature mortality resulting from disease as a surrogate measure or risk from a variety of different types of effect.

But even if this conversion of effects into QALYs or DALYs were 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 lifespan but are indicators of the overall degradation of well-being that results from various disease states. Therefore, QALYs and DALYs may be best suited for ranking and comparative analyses.

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 which 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, 2000d). Further methods development work is needed to improve the utility of QALYs and DALYs for environmental risk assessments; especially with respect to the incorporation of uncertainty (USEPA, 1999f).

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). The results of the regression analysis may provide an RfD that can reflect a variety of effects. Furthermore, the probability of experiencing effects associated with a particular severity category at doses above the RfD can be determined. To date, categorical regression has been applied to data for individual chemicals and has been used to compare chemicals with similar effects (see Dourson et al., 1997 and Teuschler et al., 1999). The use of categorical regression as a tool for combining disparate effects will require considerable methods development research.

4.1.3.2. Translating Adverse Effects into an Index

Although methods such as described in the previous section have been used in screening, ranking, and priority-setting exercises, EPA currently uses no health risk assessment procedures for regulatory analyses that combine dissimilar toxic endpoints. The Superfund program uses a screening tool (USEPA, 1989a) that combines all risks using a Hazard Index formula. Any situations where acceptable risk cannot be assumed are further assessed by separating the toxic endpoints. EPA has used “decision indices” based on dissimilar measures, and while they do not produce risk estimates, the indices still prove useful. The approach involves developing a composite score – or index – from measures of various risk dimensions (e.g., public deaths, occupational deaths, and morbidity).

Fischhoff et al. (1984) provide 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 it more appropriate for ranking and comparative analyses.

Various environmental risk indices have been developed and applied to ranking and comparative analyses. Often, these indices employ surrogate measures for risk rather than using actual calculations of the probability of adverse effects. One such index is the Hazard Ranking System (HRS) [47 *Fed. Reg.* 31219, dated July 16, 1982, and amended 55 *Fed. Reg.* 51532, dated December 14, 1990], used to place uncontrolled waste sites on the National Priorities List (NPL) 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, all scored and combined into one numerical indicator of overall hazard potential. Such an approach for a composite index has been suggested for communication of cumulative risk (Hertzberg, 2000).

Recently, EPA has been working on several index-based approaches to dealing with cumulative risk issues. EPA Region III and the Office of Research and Development have been jointly working to develop a Potential Risk Indexing System (USEPA, 1993c, 1995c, 1997b). This index also uses a vulnerability index, and 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.

EPA's Region VI 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 to evaluate the health of an area and its ecosystem/human populations. Each criterion, which leads to an indexing of 1-5, has been through the deliberative process, peer review, and is well documented.

Combining diverse effects and risk using either common metrics or indices each have pros and cons. A weakness of the index approach is that information is "lost," and the meaning of the final score can be obscured, by aggregating dissimilar information through index scores. One strength, however, is common to both approaches. Both techniques have the ability to incorporate social values in an explicit and quantitative manner in the risk assessment. 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 (1984), public concern was incorporated as an adverse effect. This 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 in an overall assessment of well-being will be critical.

4.1.3.3. Other Approaches

Another way that cumulative risk may be expressed is as margins of exposure (MOEs). Margins of exposure, defined as the no adverse effect level (NOAEL)[15] divided by estimated exposure, give a sense of how close estimated exposures in a situation might be to levels that could cause harm.. Much like a hazard index, they provide perspective, but without providing a statement of the probability of effects occurring if the exposure is greater than the NOAEL. MOEs can be used as an indication of possible risk, and can be mathematically combined across routes of exposure. The advantage of using MOEs for expressing risk is that one can preserve the route-specific nature of the different exposures and then add them to generate a total MOE. The inverse of the different pathway MOEs are added together and then the inverse of that sum is taken as the total MOE (USEPA, 2000i)

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[15] Other points of departure, such as the benchmark response (see USEPA, 1996c, 2000h), may sometimes be used instead of the NOAEL.

Collapsing the various measures of risk into a single entity (whether a common metric or index) may not be appropriate in every case. The inability to construct or inappropriateness of constructing a single numeric does not necessarily preclude the preparation of a cumulative risk assessment. As long as the disparate measures of risk can be presented in a manner that conveys a sense of the combined well-being of a community or population, the goals of cumulative risk assessment can be achieved. Geographic Information Systems (GIS) and related mapping techniques (e.g., Environmental Defense, 2001) appear to hold some promise as tools for presenting integrated information concerning cumulative risks without mathematically combining disparate measures. As with the common metric and index approaches, however, considerable methods development work remains to be completed.

4.1.3.4. General Issues with Combining Risks

As described above, each approach to portraying the results of a cumulative risk assessment has benefits and disadvantages. While common metrics and indices can incorporate social values in an explicit and quantitative manner, the meaning of the final measure can be obscured by aggregation of dissimilar effects. The abstract meaning of the final measure could lead to difficulties when communicating the results of the cumulative risk assessment to the public. Graphical and mapping techniques do not necessarily overcome such problems with communication. While these techniques may avoid some of the problems associated with the mathematical aggregation of dissimilar effects, it can be difficult to accurately describe the information a graphic is intended to convey.

The ideal with regard to cumulative health risk assessment may be when we can make projections about the potential for a particular complex exposure to cause particular effects to different physiological systems, and integrate these projections into a qualitative characterization of potential overall impact to human health.

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, can incorporate social values, are easy to communicate, and provide an integrated portrayal of the overall well-being of a community and its various subpopulations.

4.2. Risk Description

The ultimate useable 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 is synthesized that is complete, informative, and useful for decision-makers. The nature of the risk characterization will depend on the information available, the regulatory application of the risk information, and the resources (including time) available. It is important to identify and discuss all major issues associated with determining the nature and extent of the risk. Further, the EPA Administrator's March 1995 *Policy for Risk Characterization* (U.S. EPA, 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.

The 1995 *Guidance for Risk Characterization* (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 recently published a handbook on risk characterization (USEPA, 2000c).

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 decision-makers, 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.

Risk assessments are intended to address or provide descriptions of risk to one or more of the following: (1) individuals (including highly susceptible individuals) exposed at average levels and those in the high-end portions of the risk distribution; (2) the exposed population as a whole; and (3) important subgroups of the population such as highly susceptible groups or individuals (e.g., children), 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 conditions), socioeconomic (e.g., nutrition), or demographic variables, or 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.

4.3. Uncertainty Analysis

In their 1990 book *Uncertainty: A Guide to Dealing with Uncertainty in Quantitative Risk and Policy 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 & Henrion's "Ten Commandments" 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.

Although all of Morgan and Henrion's "ten commandments" are commendable, and several have been discussed elsewhere in this Framework, we should look more closely at numbers 6-8 in the box at right for some insight into uncertainty analysis. There are many resources available which talk in detail about how to perform uncertainty analysis (e.g., USEPA, 1997c, Morgan and Henrion, 1990). While we believe that detailed instruction on how to perform uncertainty analysis to be beyond the scope of this Framework, we believe that a discussion of some general principles are in order.

Cumulative risk assessment will usually be used in a decision-making process to help inform the decision-maker(s). For this reason, it is important that the decision makers be made explicitly aware of any assumptions that may significantly affect the conclusions of the analysis (item #6 in the box above). Morgan and Henrion suggest that these assumptions include:

- the main policy concerns, issues, or decisions that prompted the assessment to be done;
- 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). [adapted from Morgan and Henrion, 1990]

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" assumptions can many times contribute more to the overall uncertainty of the assessment than the factors more easily quantified.

In item #7 in Morgan and Henrion's "ten commandments," they list three types of uncertainty that analysts should explicitly include:

- uncertainty about technical, scientific, economic, and political quantities (e.g., quantities like 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?);
- 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 Item #8 in the box on the previous page, Morgan and Henrion suggest that an assessor needs to find out which assumptions and uncertainties may significantly alter the conclusions, and that process can be done using sensitivity and uncertainty analysis. Techniques for these 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.” (Morgan and Henrion, 1990)

4.4. The Information Provided by Cumulative Risk Assessment

It is important to clarify how cumulative risk assessment and this Framework document relate to community assessments and community decision making. Certainly, the Agency’s *Risk Characterization Handbook* (USEPA, 2000c) emphasizes that whatever information is imparted, it be transparent, clear, consistent, and reasonable. In simple terms, what can a cumulative risk assessment tell us, and what can’t it tell us?

4.4.1. Making Sense of Multiple Stressor Effects

The information provided by cumulative risk assessment is only a portion of the information that communities and governments need to make informed decisions about risks. It should not be the *only* consideration in decisions. There are almost always additional factors to those considered in the assessment that affect health in a community (e.g., crime, drugs, health care access, vehicle safety, climate, infectious disease, diet...). Community decision-making will also take into account risks to the environment, and consideration about historical and cultural values, as well as questions of fairness and distribution of risks. The methodology is not currently well established to take all of these factors (stressors) into account in cumulative risk assessments.

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

The Framework document 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 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*. The Framework document devotes considerable time to a discussion of improving the methods for a single part of 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 questions posed by stakeholders or interested parties. This does not mean, however, that they can’t 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.

4.4.2. Cumulative Risk Assessments in a Public Health Context

The public, in a variety of forms, continually draws attention to health statistics, asking for clarification of the relationship between environmental pollution (and risk assessments concerning it) and public health. It is important to clarify 1) that to draw relationships between environmental pollutant exposures and disease incidence, a body of epidemiological study is necessary, and 2) trying to "work backwards" from health statistics to risk factors requires full knowledge of the risk factors associated with the relevant disease(s).

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 would fall short of being able to include an evaluation of the magnitude and interactions of *all* stressors and effects. At best, the risk estimates of a cumulative risk assessment will reflect *some* of the risks which may be reflected in community health statistics. With rare exceptions[16], cumulative risk assessment estimates would not be expected to match exactly with community health statistics, even for specific health endpoints such as specific cancers.

4.4.3. How Scope and Purpose of the Assessment Affect Results

Historically, the Agency's risk assessments were usually aimed at assessing the risks of environmental pollutants to public health or the environment, for the purposes of prioritizing risk management activities or triggering regulatory action. Although there was a wide variety of specific pollutants – chemical, biological, radiological, noise – these were evaluated separately and each in the context of being protective of public health or the environment. Given the need for public health protective decisions, traditional risk assessment tools usually yield "upper confidence level" and not "best estimates" of cancer risk, and are not designed to predict risk of noncancer disease. Additionally, the many environmental pollutants comprise only some of the categories of risks to public health. When public health risks are viewed from a population-based perspective, many of the traditional risk assessments, while being quite adequate for answering the questions for which they were commissioned, leave large gaps in understanding place-based (community) public health issues. The Agency is doing more place-based

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

assessments (both human health and ecological) than in the past, but it will be some time before place-based assessments become commonplace. Even with more cumulative risk assessments being done as time goes by, initial efforts may also be largely driven by specific risk management needs and not driven by exactly the same questions that a community would ask when inquiring about local health concerns. For this reason, users of cumulative risk assessments are advised to carefully study the scope and purpose of the assessment at hand, and determine whether it is suitable (or partly suitable) to answer questions outside its stated scope and purpose.

Finally, much of the activities and data needed for cumulative risk assessment overlap with the jurisdiction of other public health agencies, and academia. The most successful cumulative risk assessments of the future are likely to 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.

4.5. Using the Results of the Assessment

Once the results of an assessment are in hand, the assessment participants will usually focus primarily on the 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 framework for what possible actions might be taken at this point.. A detailed discussion of the use of the results of a cumulative risk assessment is beyond the scope of this document, but in deciding on a course of action, other considerations will need to be taken into account along with the results of the cumulative assessment.

As discussed in the Introduction, the results of the assessment should speak directly to the question or questions addressed in the purpose for doing the assessment. Results from cumulative risk assessments can also serve a variety of other purposes, however. Results may also be used to meet regulatory mandates, to identify targets for enforcement actions, or to shape policy and regulation. They may be used for general educational purposes not directly related to an immediate decision on a course of action. Assessment results can also be used to set priorities for voluntary or regulatory action, or to mobilize community efforts to address concerns.

If the goals of a cumulative risk analysis are to estimate the total risk from multi-chemical and multi pathway exposure to individuals living within a geographical area of concern, then an important objective is to identify the major risk contributors in order to understand the sources, pathways, and stressors which 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 which most contribute to the population's risk.

If action to mitigate or prevent risk is the goal of the stakeholders, then options for action discussed in the planning of the assessment can be re-evaluated in light of the results of the assessment. Some of the issues after re-evaluating the action alternatives might 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 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 results of a risk assessment will help to keep expectations in line with possibilities.

Finally, it is important to keep in mind that the results of the risk assessment will be only one of the factors that will need 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 risk information, by itself, can not and should not determine the decision. Factors such as the availability of resources for change, fairness and other community values, politics, business and employment considerations, quality of life issues, concern for future generations, etc., will also influence any decision made. In the siting example mentioned above, the assessment may determine that the new facility does not significantly increase risk to the community and a decision not to site the facility might still be made on the basis of a quality of life issue unrelated to risk. Or, in contrast, 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. This can include both the environmental risks not covered in the cumulative risk assessment as well as the non-environmental risks that may affect a community. With limited resources, a community may use all available risk information to most effectively target its resources.

5. GLOSSARY

[to be added]

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APPENDIX A: A RESOURCE LIST FOR METHODS RELEVANT TO EXPOSURE ASSESSMENT

[Note to reviewer: Appendix A is incomplete and is actively being developed]

The following is a brief discussion of where to find some of the methods for assessing exposures to specific sources and stressors. This is not meant to be an exhaustive list, but is provided to assist the assessor in finding recognized methods for dealing with certain parts of an assessment. This list is a starting place for assessors, not a comprehensive guide to risk assessment. It is not envisioned that all cumulative risk assessments will need methods for assessing all of these sources, stressors, and pathways. Furthermore, the specific methods mentioned below may not be adequate for some cumulative risk assessment situations. Finally, new methods are constantly being developed as the state of science progresses; it is the responsibility of the assessor to determine the currency and applicability of methods used for a given assessment.

A.1. Resources Relevant to Chemical Exposures

General guidelines: [to be completed]

Air-related sources and activities: The methods for evaluating air-related exposures generally start with compiling an emissions inventory, then air modeling augmented by monitoring data. EPA's Clearinghouse for Inventories and Emission Factors (CHIEF) website (www.epa.gov/ttn/chief/) is an excellent starting place that has many of the relevant documents on methods and data for constructing emissions inventories available for download. These include *Handbook for Criteria Pollutant Inventory Development: A Beginner's Guide for Point and Area Sources* (USEPA, 1999i), *Handbook for Air Toxics Emission Inventory Development, Volume I: Stationary Sources* (USEPA, 1998g),and *Compilation of Air Pollutant Emission Factors* (for both stationary and mobile sources) (USEPA, 1995d, 1996d, 1997d, 2000f), as well as many other documents and software. Likewise, the Support Center for Regulatory Air Models (SCRAM) site (www.epa.gov/ttn/scram/) provides extensive information on the models discussed in *Guideline on Air Quality Models* (USEPA, 1999a), including downloadable software and users guides for many of the models. The Ambient Monitoring Technology Information Center (AMTIC) site (www.epa.gov/ttn/amtic/) contains information on monitoring programs, monitoring 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 the above.

Water-related sources and activities: [to be completed]

Sources to land, and waste-related activities: The EPA Office of Solid Waste and

Emergency Response has published an extensive catalog summarizing their publications (USEPA, 2000g). They have also published a "peer review draft" document called *Human Health Risk Assessment Protocol for Hazardous Waste Combustion Facilities* (USEPA, 1998h) which deals with how to assess risks from hazardous waste incinerators. These reports are available on-line.

Chemical accidents, transportation-related spills: In a population-focused assessment such as a community-based cumulative risk assessment, the threat or risk from chemical accidents may be an important factor in the assessment. Spills or other transportation-related accidental releases of materials could cause very severe short term pollution episodes and could contribute to longer term pollution. In addition, the increased likelihood of vehicular accidents could directly affect local residents. Appendix B describes the kinds of analyses conducted to determine the degree of human exposure (both to workers and the general public) associated with accidental releases of chemicals, with appropriate references.

A.2. Resources Relevant to Exposures to Non-Chemical Stressors

Biological stressors: [to be added]

Radiological stressors: [to be added]

Noise, vibration, and congestion: Increases in noise levels, e.g., from truck and/or rail traffic, could result in increased stress to local residents, as could the additional traffic congestion. Increased vibrations from additional truck or rail traffic could also increase or accelerate damage to local roads and other structures such as residences (foundation cracks), water and sewer lines, etc.. These types of damage could result in additional costs and stress to the local population. The U.S. Department of Housing and Urban Development 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 called *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.

Odor: EPA's Office of Wastewater Management has issued a report called *Guide to Field Storage of Biosolids* (USEPA, 2000e) 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.

Other non-chemical stressors: [to be added]

APPENDIX B: ASSESSING ACCIDENTAL CHEMICAL RELEASE EXPOSURE

There are several steps in assessing an accidental chemical release exposure. The typical analytical steps in an overall accidental chemical release risk assessment are process analysis, likelihood or frequency of accidents, source term modeling, dispersion or consequence modeling, and the exposure assessment.. A brief description of each step is provided below. Each of these steps can be evaluated quantitatively or qualitatively.

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). For example, if a process temperature control fails, allowing pressure to build in a reactor system, an emergency pressure relief valve may open, venting chemical to the atmosphere. More severe hypothetical scenarios are often also evaluated, such as the failure of a storage tank, leading to a massive spill. Several formal PHA evaluation techniques are available including “What-If,” “Failure Mode and Effect Analysis,” “Event-Tree”, or “Fault-Tree.” (USEPA 1998c, 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. For example, equipment failure rate data or accident histories can be used to judge how frequently certain accidental releases might occur.

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 1998c, USEPA 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. In this step, the consequences associated with those predicted releases can be evaluated. If the chemical released is a gas and toxic by inhalation, the consequence assessment would involve an analysis of the downwind dispersion, or the distance the chemical will travel downwind to a particular toxic concentration. If the chemical is flammable, the consequences of an explosion or fire might be analyzed. 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 1999d, AIChE 1996, USEPA 1993a). 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)[17], or in the *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.

The final step in a chemical accident exposure analysis is the *exposure assessment.* The exposure assessment 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. The endpoint reflects the health effect of concern; e.g., if lethality resulting from an acute toxic exposure is the concern, then the endpoint would be the airborne concentration necessary to cause acute lethality. 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). These established concentrations, however, may be based on toxicity studies that are weak, derived by consensus, or may not be the most representative of actual exposure effects. Further, little is known about the chronic or long-term effects associated with an acute, non-lethal accidental exposure, so most assessments of the risk from chemical accidents focus on acute or short-term effects. Work is currently underway to develop more appropriate emergency exposure concentrations for a number of common toxic substances.

Other factors that play a role in this type of assessment, and in the dispersion analysis step above, include an evaluation of the duration of exposure, the average or range of chemical concentration in the cloud, at what portion of a cloud an individual might be exposed, the likelihood that people are present, and whether they are indoors and indirectly exposed. Often, determination of the actual human exposure dose in a vapor cloud is a complicated exercise; typical consequence analyses only identify the distance downwind for the plume to reach a particular concentration without consideration of actual human exposure, since it is the short-term, threshold type effects that are being evaluated.

[17] There are many searchable MSDS data bases on-line that can be located with most search engines.

The results of all of these steps can be combined to generate a number of measures of risk associated with accidental releases. For example, individual risk profiles can be generated to measure the acute risk as a function of distance and direction from a chemical source. Or a societal risk can be generated to determine the cumulative probability or frequency of events that cause fatalities, injuries, or exposures over time.

APPENDIX C. DATA QUALITY ISSUES IN MONITORING AND OTHER EXPOSURE-RELATED DATA.

There are a number of separate and important issues associated with input data quality when doing a cumulative assessment. Three of these issues are: 1) data quality needed for the assessment, based on how the data will be used; 2) the relative quality of available data from various sources; and 3) combining data of different quality in a single assessment.

The Data Quality Needed for the Assessment. The level of data quality necessary for a individual assessment is an issue that cannot be overlooked. The level of certainty needed for the decision to be made relates directly to using appropriate data and analytical techniques for assessments. For a cumulative risk assessment, this means that the type of assessment – and therefore the level of certainty required – should be determined before beginning the assessment.

From the planning and problem formulation phase of the assessment, the type of assessment and depth of the assessment (i.e., screening, in-depth, etc.) should be known. Depending on the type and depth of assessment, the nature of the analytical tools used, and the quality and breath of the input data needed, can be quite different.

The Quality of Existing Data. Often when doing an assessment, it is difficult or impossible to collect new data due to time, financial, or other constraints, and the assessor must depend upon existing data bases for analysis purposes. Appendix D gives some considerations about the quality of the data found in frequently used data bases.

Combining Data of Different Quality. The assessor will encounter, and most likely use, data of differing quality when doing cumulative risk assessments. This raises the concern that the value and benefit of high quality data might be lost if combined with lower quality data. The Office of Pesticide Programs asked its FIFRA Scientific Advisory Panel (SAP) in 1999 how this issue should be addressed. The SAP (FIFRA SAP, 2000) recommended the following approach for cumulative risk assessment for pesticides:

- Clearly document the quality of the data and input parameters used in the risk analysis. Quality thresholds could be established for data use. Monitoring data, properly accounted for measurement errors, are preferred over screening level inputs.

- Focus on individual-based analysis to ensure capturing the high exposure and sensitive individuals and account for cross-media transfer and "para-occupational" exposures.

- Cumulative risk analysis should retain the resolution of geographic, temporal, and demographic variations while maintaining optimal data usage with respect to the increasing uncertainties associated with lowering of sample size.

- Systematically conduct quantitative sensitivity and uncertainty analysis for both the exposure and the toxicity.

- Uncertainties in data can be reduced or better characterized by (1) comparing sets of similar data collected from different years and locations, (2) comparing results from screening level analyses with more refined analyses from data-rich cases for selected chemicals and pathways, and (3) maintaining the association between the pathways.

- Develop the process for reassessment as new quality data become available.

APPENDIX D: SOME THOUGHTS ON QUALITY OF DATA IN VARIOUS WIDELY-USED DATA BASES

The following paragraphs contain some considerations when using data in commonly-used databases. Over the past two decades, data in environmentally-related databases has improved, but it is far from perfect. Some of the issues with databases discussed below may improve, even in the short term. The paragraphs below are meant to cause an assessor to think about specific aspects of the data being used for an assessment, and weigh the uncertainty involved in using those data.

First, there are important limitations with respect to characterization of hazardous releases to the environment. Point source release data may be based on actual measurements (e.g., Permit Compliance System [PCS] data) or estimates (e.g., Toxics Release Inventory [TRI] data) that can be inaccurate by a factor of 2, 5, 10 or even more. The availability and quality of permit data will vary geographically. Data on a significant percentage of permitted discharges may be unavailable or of poor quality due to insufficient monitoring of releases. Finding accurate non-point source release information of hazardous chemicals is especially problematic. The combination of these problems, along with the possible existence of non-permitted discharges, can make the quantitative assessment of risk a difficult task. In addition, many of the risks to the environment may not be tracked in databases (USEPA 1990b). These include motor vehicle emissions, non-TRI point sources, area sources (such as gas stations or dry cleaners), consumer product use, pesticide use, and others.

Second, for many types of analyses, the sources of pollution or the adverse environmental conditions that are to be evaluated must be assigned to specific geographic locations. A number of alternatives can be used to locate sources. The locations of monitored facilities and remediation sites are collected by the EPA, by state and local environmental agencies, and their contractors, and are available through many systems. The use of self-reported location data by regulated operators has been a common method used to acquire geographic coordinates for sites, facilities, areas, and regions of environmental concern, but analysis of the location data in EPA's data bases has shown sufficient inaccuracy to require the issuance of a Locational Data Policy (LDP) (US EPA, 1991a). The LDP mandates preferred location data collection methodologies, as well as defines accuracy and verification procedures, and the reporting of location data for regulated entities. Superfund sites and other facilities that encompass large areas typically do not have a single point of toxic material release (e.g., a single smokestack), and their recorded location coordinates may represent the administrative location of the facility (front gate, property centroid, or other office locations not even at the same site), not at the point where the pollution is occurring. *Most uses of locational data for assessments employing geographically-based models will require verification of reported data.* At a local level, this is less difficult than when doing regional or national assessments, but it can still be time consuming (and difficult if complex facilities choose not to cooperate).

Third, most existing non-GIS-based program systems cannot easily accommodate irregularly shaped area features, nor offer a complete set of documentation on the accuracy of the data already collected. The diversity of EPA's programmatic database systems in terms of their design and implementation makes it technically difficult and expensive to integrate location (and associated attribute) data across program (multi-media) lines. Also, much of the location data are collected independently by federal, state and local agencies, and according to different criteria and methods, and can be held in either hard-copy or electronic forms, or both, in a variety of locations.

Fourth, when using TRI data for cumulative risk assessments, it is important to recognize that the TRI data base only contains data on larger facilities (both in terms of number of employees and amount of materials involved), on a limited number of chemicals, and on specific manufacturing sectors. Additional sources of release data may therefore be required for a more complete assessment of risk.

Fifth, when using AIRS Facility Subsystem (AFS) release data for risk assessment, the assessor must be aware that most AFS facilities prepare emissions inventories only once every five years. It is therefore possible that the emissions data recorded in the AFS are somewhat out of date. Also noteworthy is that release information is generally available for only five criteria air pollutants: SO_2, NO_2, CO, O_3, PM-10, and Pb. Release estimates can be made for many other toxic chemicals using a model available from the Office of Air and Radiation (USEPA 1999a). Use of this model, like other models, provides additional information to the analyst, but also introduces greater uncertainty to the analysis being performed.

Finally, the Permit Compliance System (PCS) distinguishes between major discharges and minor discharges based on potential threat to health and to the environment, but most often that differentiation was made solely on the basis of relative volume of water discharged and not on the amount or nature of the toxic chemicals contained in the discharge. Only discharge information from major facilities are required to be entered into the PCS, and so minor facilities are under-represented. Some PCS records only indicate the corporate address rather than give information on the actual location of the toxic material release point, and some only show the location of the principal facility and not, when they exist, secondary facilities.

APPENDIX E: SOME THOUGHTS ON BACKGROUND EXPOSURES

When looking at aggregate exposures or cumulative risks of citizens, so-called "background exposures" to specific chemicals are no less "real" exposures than the pollution usually studied for regulatory purposes. Whereas in historical single-chemical assessments done 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 are rarely irrelevant with cumulative risk assessments[18].

Background concentrations can be categorized as either *naturally-occurring*, that is, chemicals which 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 non-point sources.

Assessments of morbidity incidence and death rates, market basket surveys, and pesticide

[18] The word "background" is often used in 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 remains 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.

residue surveys also provide information which 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 occur 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. Since cumulative risk assessments are population based, exposures due to naturally-occurring background concentrations should usually be of importance.

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 areas for designating as "background" 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 PAHs, 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 F: RESEARCH AND DEVELOPMENT NEEDS

The *Framework for Cumulative Risk Assessment* is intended to serve as initial guidance, providing a basic structure for the issues and defining key terms and concepts. In some cases, the concepts introduced in the *Framework* 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 *Framework* document, 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.

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 will involve developing an understanding of how the sequence and timing of exposures influence the ultimate risk of 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 which recognize the need to understand the timing of various exposure events (e.g., Calendex, APEX, Lifeline, SHEDS, and CARES).

In addition to gaining a better understanding of the sequence and timing of routine exposures and their relationship to effects, it is important to understand how acute, non-lethal 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 needs to be well characterized. Both measurement techniques (at the receptor) and predictive models are applicable in this characterization.

EPA's *Guidance for the Health Risk Assessment of Chemical Mixtures* (USEPA, 2001a) 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 to assess stressors in groups. Currently, however, this approach is not practicable when considering a large number of diverse stressors, since appropriate biomarkers for many types of stressors have not yet been developed.

Considering Hazards Presented by Non-Chemical Stressors

Cumulative risk assessment could encompass the interactions of chemical stressors with biological stressors, physical stressors, ecological stressors, radiological 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 to understand 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. Assessing levels of stress and their potential contribution to risk, however, is difficult for a variety of reasons. The Agency for Toxic Substances and Disease Registry (ATSDR) began the process of identifying research needs in this area through an expert panel workshop held in 1995. There is need for followup research in this area.

Considering All Aspects of Vulnerability

The issue of the vulnerability of a population can be thought of as having four components: susceptibility/sensitivity 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 it represents the integration of effects from stressors acting together. 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.), indices (e.g., Hazard Ranking System, etc.), and the categorization of effects (e.g., as for categorical regression). Alternatively, Geographic Information Systems (GIS) 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.